CLINICAL TROPICAL MEDICINE

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CLINICAL TROPICAL MEDICINE

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To the quest of knowledge which will relieve suffering and prolong life

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FOREWORD

THE RANK AND FILE OF AMERICAN PHYSICIANS AND MEDICAL students have until now felt no urge to familiarize themselves with exotic and tropical diseases and have had little encouragement or opportunity to do so War has suddenly brought a departure from this medical isolationism There is now a pressing demand for authoritative and practical instruction in the treatment and prevention of the diseases of the warm countries Medical men who have seldom seen malaria or dysentery and have never encountered yellow fever or typhus are now facing the prospect of caring for troops and civilian workers in the tropics of America Africa and the Far East

There is now no lack of appreciation of the situation Special training courses are being provided for medical students and internes and for the new medical officers of the armed forces Pamphlets and text books are being issued to bring knowledge up to date and serve for reference in the field

The latest of these needed text books is this manual compiled by Dr Bercovitz with the assistance of a distinguished Advisory Editorial Board Emphasis is placed on the tropical diseases of greatest practical importance in the present crisis such as malaria the dysenteries typhus fever and yellow fever

The value of a manual of this kind depends on the authoritative position of the contributing scientists and it is gratifying to find among those who have taken part in the production of this volume so many persons of broad experience and scientific distinction

It is hoped that the book will fulfill its purpose of facilitating the teaching of tropical medicine and that it will also help to stimulate and perpetuate the growing interest of Americans in tropical medicine

WILBUR A SAWYER

New York N Y

PREFACE

THIS MANUAL OF CLINICAL TROPICAL MEDICINE IS DESIGNED to meet the needs of physicians who as a direct result of the war have been or will be confronted with more or less unfamiliar forms of tropical diseases It is hoped that to the general practitioner now encountering these diseases in ever increasing number and variety it will prove helpful in solving problems of diagnosis and treatment and that to the medical man stationed with our armed forces in areas where tropical diseases are prevalent it will serve as a practical handbook of prevention as well as of diagnosis and treatment This volume has also been planned to give the medical student a definite picture of tropical diseases their symptomatology pathology and the most authentic and effective therapeutic and preventive measures before he plunges into specialized monographs and controversial articles on the manifold aspects of tropical medicine

The accumulated knowledge of tropical diseases has become so extensive that it is no longer possible for one man to be expert in all the branches of this field of medicine Twenty seven scientists distinguished by their broad clinical and research experience have contributed their specialized knowledge to provide in this volume authoritative information on diarrheal diseases diseases caused by blood protozoa spirochetes spirilla rickettsiae viruses bacteria yeasts fungi helminths nutritional deficiencies and by tropical snakes and poisonous insects

The symptomatology pathology epidemiology diagnosis treatment and prevention of each disease have been discussed concisely but comprehensively enough to afford the practicing physician a clinical guide As the medical man in the field must often make his own laboratory tests with a minimum of equipment and supplies the simplest practical manner of performing and interpreting specific and necessary laboratory tests is described in workable detail

An effort has been made to evaluate the suggested therapeutic measures for each disease and to explain thoroughly the methods of application of those that have given most satisfactory results in practice To make the discussions of treatment as serviceable as possible proper dosages and methods of administering the requisite drugs have been included together with the contraindications and untoward reactions which may develop in the use of drugs

As prevention of disease is a most important phase of tropical medicine adequate space has been devoted to the various factors involved in the spread of disease the problem of eradication of insect vectors the role of personal hygiene and sanitation and the use of vaccines

CONTENTS

Illustrations have been chosen to show the typical forms and manifestations of the diseases rather than the rare case that is primarily of academic interest For permission to reproduce these illustrations I am indebted to the following Dr Clifford A Dobell for his complete set of plates of intestinal protozoa which have been reproduced exactly as originally published and form one of the most valuable contributions to this book the Wellcome Research Institution for permission to use the late Dr Balfour s plate on fallacies and puzzles in blood examinations for malaria Dr C M Wenyon Director of the Wellcome Research Institution London for his plates on malaria leishmania and trypanosomes Mrs C R Hulse of the College of Physicians and Surgeons Columbia University who placed at my disposal the original slides of microfilariae which had been prepared by the late Professor F W O Connor who before his untimely death had kindly promised them for publication in this volume Dr W W Cort and his associates in the Department of Helminthology School of Hygiene Johns Hopkins University for the preparations of *Microfilaria malayi* and ova of various helminths Dr Henry E Meleney of New York University for slides of kala azar in the hamster Dr Meleney and Dr Harry Most for a specimen of *Schistosoma japonicum* and the Royal Society of Tropical Medicine and Hygiene for the plates of thick films in malaria which were redrawn from those in original articles published by Field and Flemming in the *Transactions of the Royal Society of Tropical Medicine and Hygiene*

I am especially grateful to the members of my advisory board Dr W W Cort Col Charles F Craig and Col Edward B Vedder for the many hours they have devoted to the painstaking study of the manuscript and for their stimulating criticism and generous advice and to Dr Henry E Meleney for his personal interest in the preparation of this work and for his frank and constructive suggestions which has served as a constant source of stimulation and encouragement I wish to thank the Advisory Committee on Publications of the Department of Medicine New York Post Graduate Medical School Columbia University and Captain Robert Clinton Page Medical Corps United States Army for reviewing the entire manuscript

I am indebted to Dr Marion Osborn for editorial aid and to Miss Nettie Rosenberg for editorial aid proof reading and preparation of the index

I wish especially to express my appreciation to those associates and friends whose valuable suggestions and generous help made the publication of this work possible

Z TAYLOR BERCOVITZ

New York N Y

SECTION ONE

THE DIARRHEAL DISEASES

CHAPTER 1

INTRODUCTION

Z T BERCOVITZ

THE TERM DYSENTERY DESIGNATES IN TROPICAL COUNTRIES a symptom complex with which are associated frequent evacuations of the bowels with or without blood and mucus

The diarrheal diseases that are commonly seen in tropical countries and that are related to specific infections may be grouped under three major headings

I Bacterial
   1 The bacillary dysenteries caused by organisms of the *Shigella dysenteriae* group Shiga Flexner and Sonne

II Protozoal
   1 Amebic dysentery (*Endamoeba histolytica*)
   2 Balantidial dysentery (*Balantidium coli*)
   3 Flagellate dysentery (possibly *Giardia lamblia*)
   4 Plasmodial dysentery (malarial dysentery)

III Helminthic
   1 Bilharzial dysentery (*Schistosoma mansoni* *Schistosoma haematobium* or *Schistosoma japonicum*)
   2 Verminous dysentery (*Aesophagostomum apiostomum* or *Aesophagostomum stephanostomum*)

The outcome of the treatment of any case of diarrhea depends largely on the correctness of the diagnosis and accordingly on the application of proper specific therapeutic measures Thus when dealing with diarrheal conditions especially among troops or large groups of individuals the physician must make the correct diagnosis promptly Other conditions that may be present but that may not be related to tropical diseases such as carcinomatosis of the bowel or diverticulitis must always be borne in mind

Other species of non pathogenic amebae have since been recognized including *Iodamoeba butschlii* (Prowazek 1911) *Endolimax nana* (Wenyon and O Connor 1917) and *Dientamoeba fragilis* (Jepps and Dobell 1918)

ETIOLOGY

Amebiasis is caused by *E histolytica* which gains entrance to the human body with the ingestion of contaminated food or water (The parasite is described in detail and fully illustrated in Chapter IV) Cyst forms of the parasite contaminate food supplies and infect water and when ingested they pass through the stomach to the upper intestinal tract They establish themselves in the mucosa and submucosa where they attack surrounding cells

Since *E histolytica* is a true tissue parasite it cannot flourish in other media Of its three life forms only the cysts can survive for any length of time outside the human host Trophozoites die as soon as the feces dry whereas the cyst wall protects the cyst forms and enables them to live for as long as three weeks in the fecal matter They are able to resist ordinary disinfectants to a remarkable degree while chlorination of water leaves them unharmed Thus the cysts of *E histolytica* possess the survival qualities necessary to enable them to find other human hosts once they have been dislodged from their habitat

The control of cyst passers constitutes the central problem in dealing with amebiasis as it is from the bowel discharges of these individuals that cysts are free to infect food and contaminate water supplies

EPIDEMIOLOGY

Epidemiology is concerned with the dissemination of the cysts of *E histolytica* not only by the fingers and finger nails of cyst passers but also by flies feces and uncooked foods

Transmission by Flies Flies play a major part in the transference of cyst laden feces to food and water It has been discovered that houseflies can carry cysts in their intestinal canals and that they pass them unchanged in their excreta The most satisfactory method of destroying cysts in food or water is to boil everything destined for human consumption for at least thirty minutes In areas in which amebic dysentery prevails it is desirable to boil all drinking water to avoid eating cold native foods to eat only hot cooked foods and to wash the hands freely with soap and water before handling food that is to be eaten

Transmission by Water Water is one of the important media in the transmission of amebic dysentery Especially in tropical countries all unprotected wells and tanks are probable sources of danger

The Chicago epidemic of 1933 was the first recognized water borne outbreak of amebic dysentery as well as the only known extensive epidemic of this disease The source of infection was the water supply which was shared by two hotels A defective plug in an overhead sewer permitted leakage of the pollution into a drinking water tank below The number of cases of amebiasis

CHAPTER II

AMEBIASIS

Z T BERCOVITZ

AMEBIASIS IS PRIMARILY AN INTESTINAL DISEASE CAUSED BY the tissue parasite *Endamoeba histolytica* This protozoan organism is an ameba that seeks to establish itself in the human body to which it gains entrance through the intestinal tract From cysts ingested with contaminated food and water motile trophozoites of *E histolytica* are liberated into the lower ileum and upper regions of the large intestine These amebae make their way into the tissues of these organs where they give rise to the widely varied clinical symptoms that constitute amebiasis

HISTORICAL NOTE

In 1875 Losch found an ameba in the stool of a Russian patient who was suffering from acute dysentery After the patient died he found the same parasite which he called *Amoeba coli* in the intestinal tissues Kartulis (1886) and Councilman and Lafleur (1891) proved that *A coli* was responsible for the symptoms noted in a type of dysentery prevalent in tropical countries as well as in the tropical liver abscess

In 1893 Quincke and Roos noted that there were morphologic differences between the *A coli* found in this dysentery and the protozoan organisms found in other intestinal diseases as well as in normal health Ten years later Schaudinn gave the first clear description of these amebae He showed that two different species inhabited the human intestine one identical with Losch's *A coli* and responsible for ulcerative lesions of the intestines and one apparently causing no pathologic condition which other observers (notably Casagrandi and Barbagallo 1895) had noted in the lumen but not in the tissues of the bowel Schaudinn therefore named the pathogenic ameba *Endamoeba histolytica* and the non pathogenic organism *Endamoeba coli* In morphologic structure however these amebae were found to resemble so closely members of the genus *Endamoeba* (established by Leidy 1879) that the International Commission on Zoological Nomenclature ruled that *Endamoeba* was the appropriate generic name for the amebae described by Schaudinn

Lesions caused by penetration of the submucosa and tissues by the amebae are found first of all in the region of the ileum and cecum and then in the flexures of the large intestine The oldest ulcers will be localized in these regions but unless the infection is checked the lesions will spread over a fairly extensive area in the intestinal tract from the ileum to the rectum When examined macroscopically and microscopically these lesions present features that are characteristic of infection with *E histolytica*

Macroscopic Appearance of Bowel in Amebic Dysentery

The intestine is normally pale pink soft and velvety but ulceration of the muscular coat causes discolored areas to appear and these range in color from red and brownish yellow to black In chronic amebic dysentery of long duration marked thickening of the intestinal wall is present This thickening may be extensive or limited in area It occurs chiefly in the submucosa although it may involve other layers as well

Cytolysis and necrosis of the superficial cells of the mucous membrane accompanied by hyperemia and edema of the surrounding tissue mark the primary lesions in amebiasis These lesions which belong to the pre ulcerative stage are minute nodules usually with pin point orifices that project slightly from the folds of the mucous membrane They contain a yellowish tinged gelatinous substance composed of debris from broken down cells mucus and *E histolytica* trophozoites When sectioned these nodules are seen to be flask shaped with their base in the submucous coat of the intestine Necrosis of the mucous membrane covering the nodules gives rise to small ulcers which in turn involve the surrounding tissues If the pathologic process is not checked these ulcers extend to the muscular coat where they establish their floor Very small ulcers have sharp edges and a relatively smooth floor while the tissue surrounding them is edematous and sometimes hemorrhagic Buttonhole ulcers have narrow openings resembling buttonholes

Typical amebic ulcers are considerably raised from the surface of the mucous membrane Their edges are thickened and characteristically shaggy owing to the presence of necrotic material Older ulcers tend to have smooth floors while more recently formed ulcers have a rougher surface and are filled with necrotic substance The three types of lesions that are associated with amebic dysentery include

Nodular thickenings which are filled with viscid gelatinous material in which *E histolytica* trophozoites may be found are situated on the summit of folds of the mucous membrane

Ulcers with thickened walls and shaggy yellowish brown edges that are always undermined These ulcers are covered with a necrotic membrane their interior is filled with pus or yellowish brown material and their floor is formed by the submucous or muscular coat

Sinuses which are almost invariably present and which connect ulcers They are situated in the mucous membrane or beneath the ulcers In areas between these lesions the mucous membrane shows no change from normal If however the process is of long standing the whole bowel wall becomes

reported was 1 409 About 75 per cent of the persons affected had been at one or the other of the hotels and amebic dysentery contracted from this source was reported from about 400 cities in America The incidence of carriers among the employees of the two hotels was 37 8 and 47 4 per cent respectively There was little or no dissemination of the disease among persons other than those infected at the original source Significant information and findings in connection with the Chicago epidemic are given in the *National Institute of Health Bulletin No 166*

Transmission by Other Means Contamination of foods by fingers on which cysts of *E histolytica* have lodged is regarded as one of the most important methods of spreading amebic dysentery Fingers may be contaminated as a result of poor personal hygiene or as a result of contact with fecal matter during work Experiments have shown that cysts will remain alive under such conditions for forty five minutes but they disappear from under finger nails when the hands have been thoroughly washed

Cysts will adhere to fresh vegetables when human excreta are used as they frequently are in the tropics and Near East for manure purposes If these vege tables are consumed without being first cooked there is danger of ingesting the cysts with them

Incidence of Amebiasis and Amebic Dysentery Residence in areas in which amebic dysentery is endemic and lowered physical resistance to disease are important factors in the incidence of amebiasis and amebic dysentery No race is immune to amebic dysentery

Geographical Distribution of Amebiasis and Amebic Dysentery Amebiasis and amebic dysentery are world wide in distribution Indeed so widespread are they that individuals infected with *E histolytica* have been found in every locality in which surveys have been made They are of course most prevalent in tropical and subtropical regions where conditions favor the parasite but are frequently found in temperate climates and are not unknown in cold countries

PATHOLOGY

Establishment of *E histolytica* in the intestinal tract gives rise to a pathologic condition The seriousness of that condition is determined by the severity of the infection and by the ability of the intestinal tissues to withstand the harm ful effects caused by the presence and activity of the parasite Cysts of *E his tolytica* ingested with contaminated food or drink pass through the stomach to the small intestine Here motile trophozoites are liberated from the cysts and these forms establish their habitat in the lower ileum and upper large intestine They invade the local tissues by means of their vigorous motility and of the cytolysin which they excrete and which enables them to break down the tissues Once within the tissues they have ideal conditions for continuing their life cycle Those which remain in the lumen of the in testinal tract do not thrive so well when conditions become too unfavorable they go through the precystic stage and then form cyst walls after which they pass out of the system with the bowel discharge

thickened and is characterized by fibrosis while the sinuses connecting the ulcers become deeper and more numerous

Microscopic Appearance of Bowel in Amebic Dysentery

E histolytica trophozoites can be demonstrated in sections of invaded intestinal tissues but cysts have never been observed Edema infiltration of

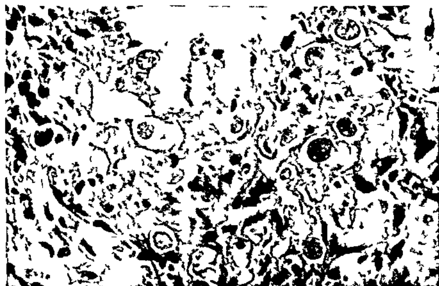


Fig 3 Amebic dysentery The same as Figure 2 but under higher magnification (× 450) showing amebae with zones of lysis surrounding them pyknotic nuclei and small round cell infiltration

lymphocytes (Fig 1) and of connective tissue cells and engorgement of the capillaries cause thickening of the submucosa Large numbers of cells show fatty degeneration and their nuclei are swollen Amebae are found near the edges of the ulcers beneath their bases in the crypts of Lieberkuhn and in the interglandular tissue The amebae gather in nests (Fig 2) where they are surrounded by necrotic tissue (Fig 3) Otherwise they lie in rows within the lymphatic spaces or frequently in veins and capillaries If there is no complicating bacterial invasion there is little or no exudation in the tissues in which the amebae are lodged Thus is characteristic of amebic infection and is *contrary to the findings in bacillary dysentery*

Cellular Exudate of Bowel Discharge in Amebic Dysentery

Studies of the cellular contents of bowel discharges in amebic and bacillary dysentery have been made by Manson Bahr Callender Bahr and Willmore Haughwout Wenyon and O Connor and others The following description of the cytology of the exudate of amebic dysentery is taken from Callender

Fig 1 Amebic dysentery *Endamoeba histolytica* infection of the colon showing ulceration of the mucosa × 100



Fig 2 Amebic dysentery The same section shown in Figure 1 but deeper in the bowel wall Note nest of amebae with areas of lysis and round cell infiltration in both sections × 100

are present in varying numbers and become less frequent as the leukocytic elements increase Their origin and nature has not been determined These *crystals should not be considered diagnostic* but they indicate the proba

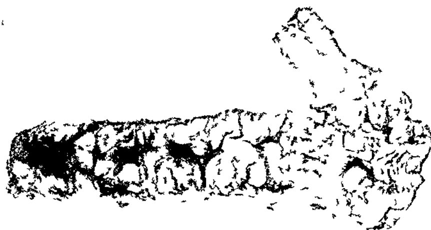


Fig 5 Amebic dysentery Gross specimen of colon (Courtesy of U S Army Medical Museum *Neg No 391 4*)

bility of amebic infection and the necessity for a thorough search concentra*tion of the stool and culture Leukocytes identifiable as such show* fading out of the cytoplasm without much change in the nucleus As the purulent character of the secondary lesions becomes more pronounced the proportion of pyknotic bodies decreases but it *will rarely be less than from 30 to 50* per cent of the basic staining elements The exudate corresponds quite exactly with the pathologic picture in the ulcer above in which the piling up of granulating membrane occurs with superficial leukocytic infiltration and exudation of pus

Sigmoidoscopic Appearance of Bowel in Amebic Dysentery

The following description of the bowel as seen through the sigmoidoscope in amebic dysentery is taken from the observations of Callender (1937) which were based on a series of 1 000 proctoscopic examinations

In amebic dysentery (Fig 5) the earliest visible lesions are small elevations in the mucosa varying in size from a fraction of a millimeter to 1 or 1 5 *millimeters in* diameter and having the appearance of a small vesicle or cyst The mucosa about the lesions presents a normal appearance At this early state of the development of the disease the cytologic characteristics of amebic *dysentery* are seldom demonstrated *If* a lesion is ruptured and the contents evacuated onto an applicator or spoon and examined immediately numerous *E histolytica* mixed with mucus red corpuscles and leucocytes

(1937) who also has summarized the available literature on the pathology of the dysenteries

When the initial amebic lesion ruptures onto the bowel surface detritus

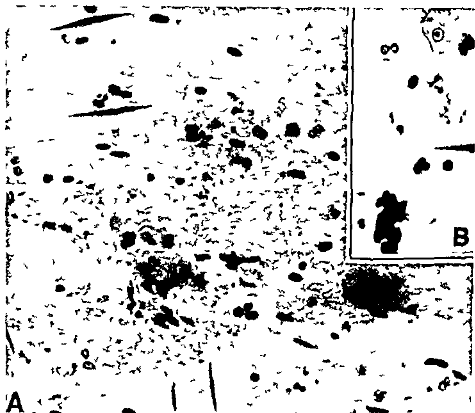


Fig 4 Amebic dysentery A Exudate in stool in early stages of exacerbation in amebic dysentery Note Charcot Leyden crystals and pyknotic nuclei (leukocytic nuclei without cytoplasm) B Clumping of red blood cells and fading leukocytic cytoplasm (G R Callender Courtesy of the *Archives of Pathology*)

degenerated and normal trophozoites and some blood are discharged but as practically no leukocytes exist at this period few or none appear in the exudate Bacterial infection causes leukocytes to appear in the tissues surrounding the abscess and to exudate into the lumen Varying numbers of amebae will also be present and the evidence of their action preponderates in the exudate seen in the stool This is indicated by the appearance of the leukocytes some 70 to 90 per cent of which consist of nuclei alone (pyknotic bodies) (Fig 4) the cytoplasm having been dissolved by the lytic action of the amebae Red corpuscles when in relatively small numbers appear in clumps as if agglutinated (Anderson s phenomenon) Charcot Leyden crystals

PATHOLOGY IN COMPLICATIONS OF AMEBIASIS

Amebic Abscess of the Liver

Amebic abscess of the liver occurs in about 5 per cent of cases of amebiasis and is the most common and most important complication of infection with



FIG 6 Amebic abscess of the liver (Courtesy of Dr S H Polayes)

E histolytica The amebae reach the liver through the portal vein The liver offers stubborn resistance to the amebae but as trophozoites are constantly borne to it under favorable conditions some of them manage to establish themselves in the liver tissue This insidious onset resulting from constant attack gradually extends until a large necrotic area is involved when this happens an amebic abscess forms The right lobe and the upper pole are most frequently involved in hepatic amebiasis But since the liver does not provide conditions favorable to the development of *E histolytica* no abscess can form unless the liver has been unable to withstand these incursions of the amebae

Macroscopic Appearance Although in some cases the liver may appear to be normal in size it is usually found to be enlarged a condition that is accompanied by fatty degeneration and congestion A large abscess (Fig 6) if

which show the characteristic lytic degenerative changes described under cytology will be found The distribution of these early lesions varies some what but they are most frequently observed (1) on the anterior wall of the rectum ° to 4 cm above the internal anal sphincter (2) on the margins of the valves of Houston and especially along the lower surface near the extrem ity of the valve just as the fold is spreading out into the rectal walls and (3) in the immediate vicinity of the rectosigmoid junction These lesions are seldom seen and when present are easily missed in routine examinations We observed them four times in a series of one thousand proctosigmoidoscopic examinations The importance of searching for the lesion and confirming the diagnosis by microscopic examination of the contents lies in the fact that by early treatment the amebic infection is more easily curbed before open ulcera tion and secondary bacterial invasion occur

In amebic dysentery as usually seen the lesions are some days older than those described above At this time the lesion is a mound in the mucosa 2 mm to 6 or 8 mm in diameter rising gradually from the periphery to the sum mit at which point the elevation is 1 to 3 mm Upon the summit of this mound there is a small crater from which exudate may be expressed Frequently a little bleeding attends or follows the expression of exudate The surrounding mucosa presents a normal appearance and the periphery of the lesion is un changed in color At the edge of the crater a mild fairly sharply defined narrow border of hyperemia may be seen There is a normal muscular reaction of the gut wall to the examination

Extension of this lesion or mucosal ulceration of the first type pro duces a larger ulcer from a half to one centimeter or more in diameter Its margin is slightly ragged and overhanging There is a narrow sharp hyperemic line of demarcation at the edge of the ulcer separating it from the surround ing normal mucosa The ulcer is saucer shaped and the bottom is commonly covered with a dirty gray membrane which when wiped away leaves a bleed ing surface At this stage in the development of the pathology lesions may be found in groups some of the ulcers coalescing others close together with a narrow strip of mucosa between them which often presents the appearance of inflammatory reaction without edema

These lesions are typical of amebic infection but when secondary infec tion is of considerable intensity as in the severe and moderate clinical dysen teries the picture is modified The area of reddening may increase even to the involvement of the entire mucosa but the discrete ulcerations give a clue unless the diphtheritic inflammation of Shigella dysentery masks the under lying picture

In cases characterized by extensive bleeding the ulcers may be rather nu merous and differ from those described above The intervening mucosa is essentially normal but the ulcers are covered with dark clot on the removal of which frayed tissue fills the crater or may project while bleeding is active The sigmoidoscope should be used with great care when there is much bleed ing and is contraindicated in the presence of frank hemorrhage

When no secondary bacterial infection is present the contents of an amebic liver abscess are bacteriologically sterile Anaerobes of the *Bacteroides* group may be present in amebic abscess of the liver and they are easily overlooked unless anaerobic studies are made When mixed infection is present amebic abscesses lose their characteristic appearance and resemble pyogenic abscesses which occur elsewhere in the body

Amebic Abscess of the Lung

Primary amebic abscesses of the lung are rare Lung abscesses usually follow rupture of an amebic abscess of the liver through the diaphragm into the lung or pleural cavity sometimes they follow empyema caused by rupture of an amebic abscess of the liver The lower lobe of the right lung is thus the usual site of infection with amebic abscess Within the lung abscess wall is a zone of necrotic material composed of broken down lung cells lymphocytes some polymorphonuclear leukocytes and amebae

SYMPTOMATOLOGY

The most constant symptoms in amebic dysentery include an insidious onset abdominal pain either general or localized diarrhea copious bowel movements six to eight times in the twenty four hours mucus which may be blood streaked alternating diarrhea and constipation Tenesmus is not marked as a rule

Amebic dysentery may be either acute or chronic and the symptoms may be either mild or severe

Acute Amebic Dysentery

After the ingestion of cysts of *E histolytica* the patient may show symptoms of acute amebic dysentery within a few days or not for years The onset of symptoms is usually gradual although in some cases it is very sudden When the onset is sudden the patient has acute abdominal pain and immediately begins passing stools containing mucus and blood More frequently however symptoms do not appear until after an initial attack of diarrhea which may last for one day or longer Then blood and mucus begin to appear in the stools At first stools are copious and contain a large amount of fecal matter but after a few hours they become semifluid or fluid and contain much blood streaked or blood flecked mucus They have a peculiar musty albuminous and offensive odor There are from six to eight or ten copious bowel movements in the course of twenty four hours Tenesmus is either absent or not severe in amebic dysentery and the patient is able to relax after bowel movements Fever is not marked because the patient is not toxic as in bacillary dysentery As a rule pain is generalized over the abdomen but it may be localized in the right iliac region or in the region of the sigmoid tenderness is most marked over the cecum and the sigmoid Frequently severe abdominal pain ushers in acute amebic dysentery The pain is cramplike and is located in the lower abdomen There may be colicky pains between bowel movements

present at the dome of the liver may adhere to the diaphragm and there may be marked evidence of inflammation of the diaphragm near the abscess This inflammation accounts for the relative frequency of rupture of the abscess through the diaphragm with the consequent formation of lung abscess

In addition to the amebic abscess the liver may have necrotic areas of varying size in which definite abscess formation is not visible Material taken from the wall of these areas contains motile trophozoites of *E histolytica* Sections from these areas show cytolysis of the tissue and an accumulation of fibrin lymphocytes connective tissue cells and red blood corpuscles within a connective tissue framework Amebae also are scattered throughout A hyperemic zone surrounds these areas but there is no definite abscess wall They represent the earliest visible stage in the formation of an amebic abscess namely amebic hepatitis

The contents of an amebic abscess of the liver depend on whether the abscess of the liver has been caused by amebae only or whether bacteria are also present When the abscess is caused by *E histolytica* alone it does not contain pus It is filled with a characteristic mixture of semifluid yellowish red or chocolate colored material composed of shreds of necrotic liver tissue blood and cytolysed tissue When a mixed bacterial infection is present the abscess cavity may contain pus If the abscess is due to bacteria entirely its contents consist of yellowish or greenish yellowish pus if the bacteria are present as well as *E histolytica* trophozoites the abscess will contain the material characteristic of amebic abscess as well as the pus

Because the connective tissue of the liver offers a marked resistance to cytolysis and because the invasion of the tissue by *E histolytica* stimulates the formation of connective tissue the abscess wall has a typical character when caused by the trophozoites of *E histolytica* In small abscesses the wall is visible but is not well marked whereas in older abscesses the wall is composed of dense connective tissue In medium sized and large abscesses the inner wall is covered with shreds of necrotic tissue which give it a peculiar shaggy appearance

Microscopic Appearance Sections of larger abscesses with relatively thick walls have more or less cytolysed necrotic material on the inner edge in which mononuclear leukocytes blood corpuscles fibrin and amebae are present Surrounding these is a zone of actively proliferating connective tissue cells in which there are numerous lymphocytic leukocytes This zone is enveloped by a layer of dense connective tissue which is infiltrated with connective tissue cells The whole abscess is surrounded by a zone of hyperemia This may contain small capillary hemorrhages and the branches of the portal vein may contain thrombi as well as amebae

The amebae are found in the abscess wall in the zone of necrosis generally near the border of the connective tissue zone They are not found in the dense connective tissue of the abscess wall consequently they are difficult to demonstrate in old abscesses which have thick fibrous walls and little necrotic material

When no secondary bacterial infection is present the contents of an amebic liver abscess are bacteriologically sterile Anaerobes of the *Bacteroides* group may be present in amebic abscess of the liver and they are easily overlooked unless anaerobic studies are made When mixed infection is present amebic abscesses lose their characteristic appearance and resemble pyogenic abscesses which occur elsewhere in the body

Amebic Abscess of the Lung

Primary amebic abscesses of the lung are rare Lung abscesses usually follow rupture of an amebic abscess of *the liver through the diaphragm into the* lung or pleural cavity sometimes they follow empyema caused by rupture of an amebic abscess of the liver The lower lobe of the right lung is thus the usual site of infection with amebic abscess Within the lung abscess wall is a zone of necrotic material composed of broken-down lung cells lymphocytes some polymorphonuclear leukocytes and amebae

SYMPTOMATOLOGY

The most constant symptoms in amebic dysentery include an insidious onset abdominal pain either general or localized diarrhea copious bowel movements six *to eight times in the twenty four hours mucus which may be blood* streaked alternating diarrhea and constipation Tenesmus is not marked as a rule

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these pains become more severe just before the movement and disappear after it Acute dyspepsia usually accompanies these symptoms

Chronic Amebiasis

The initial attack of acute amebic dysentery is usually followed by a period of quiescence during which there are alternating attacks of diarrhea and constipation The diarrheal stools may contain mucus and some blood and there may be a history of repeated attacks of dysentery with blood and mucus The patient may suffer constantly from tenderness over some areas especially over the ascending and descending colon and abdominal pain especially over the cecum ascending colon descending colon and sigmoid is a fairly constant accompaniment of chronic amebiasis Upon deep pressure it may be found that the entire colon is tender There is also gaseous distention of the abdomen and the patient feels a dull aching sensation in the lumbar region Even when these symptoms are absent the patient suffers abdominal discomfort and feels depressed and apprehensive In chronic amebic dysentery of long duration the coats of the intestine become thickened and the colon can be palpated easily There is sometimes a loss of weight which varies with different individuals although it is not so marked as with acute amebic dysentery

Amebiasis Without Symptoms

There are a certain number of individuals who harbor cysts of *E histolytica* and have no symptoms related to the gastro-intestinal tract at the time the infection is discovered by microscopic examination of the stools These symptomless carriers are a source of danger not only to themselves but to the community in which they live

Mild Cases of Amebiasis

About 50 per cent of the individuals infected with *E histolytica* experience mild nervous and intestinal symptoms Many of them are unaware of the fact that the occasional symptoms from which they suffer such as constipation abdominal discomfort with distention and gas occasional pain nausea headaches and mental depression are related to a pathologic condition Constipation may be chronic or it may alternate with diarrhea There may be no diarrhea at any time Attacks of diarrhea however come at relatively infrequent intervals and clear up quickly In some instances they consist of only one profuse diarrheal stool accompanied by abdominal pain Mucus is seldom present in the stools unless the attack lasts for several days and blood may be absent altogether Abdominal distention and colic are common symptoms and may be localized in the right iliac region or in the lower left side of the abdomen Attacks of acute pain in the lower right quadrant of the abdomen may simulate appendicitis but if amebae invade the appendix they give rise to symptoms of subacute or chronic appendicitis The abdomen is tender to palpation especially in the lower right quadrant where the thickened cecum is easily demonstrated Tenderness over the liver region may indicate amebic

hepatitis with or without abscess formation These symptoms are accompanied by digestive disturbances of a mild nature The appetite is uncertain nausea may be present Fever is seldom present it may accompany a diarrheal attack but it will be mild Loss of weight weakness muscle aches and pains and headache are common

Next in degree of severity are mild cases which are characterized by repeated attacks of diarrhea These attacks are severe and are more exhausting for the patient They may last for several weeks and may alternate with constipation A considerable amount of mucus is present in the semifluid or fluid stools Microscopic examination of specimens may reveal the presence of blood corpuscles although the mucus will not have a blood streaked appearance Abdominal pains may and usually do accompany these symptoms of amebiasis at any time

Carriers

The term healthy carrier is most unfortunate because all available evidence indicates that *E histolytica* always invades the tissues of its host There can therefore be no such thing as a healthy carrier Many individuals do not show symptoms of amebiasis for long periods of time although there are cysts of *E histolytica* in their stools Some have slight symptoms to which they become accustomed and consequently they are unaware of the nature of their ailment The symptoms present in the ordinary carrier include constipation occasional attacks of slight diarrhea colic in the lower abdomen or in the right iliac region anorexia gaseous distention of the abdomen after eating eructation and even slight nausea before eating or directly afterward Neuralgic pains in the lower abdomen back or legs dull aching in the muscles of the legs especially in the morning and lassitude are characteristic Vasomotor disturbances irritable pulse and arrhythmia are also present in carriers On examination carriers may be found to be underweight and to have a sallow skin The abdomen may be distended and there may be tenderness on deep pressure over localized areas of the large bowel and over the liver

COMPLICATIONS

The most important complications of amebiasis are amebic abscess of the liver lung brain and amebic appendicitis Rarer complications include invasion of the skin gall bladder and genito-urinary system with amebae perforation of the bowel intestinal hemorrhage and peritonitis

Amebic Hepatitis and Liver Abscess

Amebic hepatitis with or without abscess formation may occur in any patient who has suffered from an *E histolytica* infection even if symptoms of amebic dysentery do not appear This complication of amebiasis may develop in persons who have been free from symptoms of amebic dysentery for months or even years and in whom no cysts of *E histolytica* can be found at the time of the current illness The absence of forms of *E histolytica* from the stools does

not preclude a diagnosis of amebic abscess of the liver especially if there are other signs and symptoms present that indicate liver involvement In such cases the patient is usually underweight bilious suffering from nausea anorexia vomiting of bile stained material and constipation which may or *may not alternate with diarrhea There may be no fever and no change in the* blood count Under such conditions therapeutic tests with emetine injections may help to resolve the problem of diagnosis

The *presuppurative* stage of amebic hepatitis may continue for a variable period of time during which the liver is inflamed and tender The hepatitis may progress and become more acute with the development of fever leukocytosis and enlargement of the liver which may become very tender The *leukocyte count may reach 15 000 to 25 000 or 30 000 but the higher counts* are usually indicative of secondary bacterial invasion In the chronic forms of amebic hepatitis the leukocytosis is slight the temperature is not so high the enlargement of the liver is not so marked and there is not so much tenderness as in the acute stage

The onset of symptoms of amebic abscess of the liver is characterized by marked variations Generally pain and tenderness develop gradually in the *liver area and these are associated with increase in the size of the liver with* fever leukocytosis and general malaise In some instances the symptoms may be so slight and their development so gradual that the patient is hardly aware of his condition until the abscess is of considerable size In some individuals the first indication of liver abscess is a sharp stabbing pain in the liver region associated with rupture of the abscess either into the peritoneum or through the diaphragm into the pleura and lung Fortunately this is not common

Pain and fever are usually associated in amebic abscess of the liver although as a rule the pain precedes the fever The pain is of a dull aching or boring type but may be acute and localized over the liver area It is commonly referred to the right shoulder to the right axillary area or to the back Fever varies from 38 to 39 C (100 4 to 102° F) it is higher at night and remissions follow toward morning A high degree of fever usually indicates the presence of a complication with secondary bacterial infection

When amebic abscess is present the liver is enlarged both upward and downward The lower border of the liver may extend below the costal margin and is usually smooth tense and tender Percussion and roentgen ray examinations may demonstrate that the upper border is elevated and irregular in outline There may be a small mass the size of an egg or the irregularity may involve the greater portion of the upper surface of the liver If involvement of the liver is extensive and especially if there is a tendency for the abscess to point toward the axilla edema of the intercostal spaces is present and local bulging indicates the location of the pointing of the abscess Pain in the intercostal spaces in the right axillary area is marked and may extend over most of the region of liver dullness Over the ribs on the right side the liver is painful to pressure with the flat of the hand

The diagnosis of amebic abscess of the liver rests finally on the demonstra

tion of typical liver pus by aspiration Aspiration may be done by following the directions given under treatment of amebic abscess of the liver (page 26) Diagnostic aspiration of a liver is indicated when an amebic abscess involvement is suspected It is relatively safe in the hands of one who is experienced in the necessary technique The aspiration is generally made in the midaxillary line from the seventh to the ninth interspace depending on the point of greatest tenderness edema or bulging Liver pus is thick viscid dark brick red or chocolate-colored streaked or mixed with blood and here and there clear mucoid or yellowish material The pus is so thick that it is not absorbed readily by the dressings It may contain bits of necrotic tissue *Endamoebae* are not usually found in freshly aspirated liver pus or in the material that escapes at operation but after a few days they appear in the discharge from a drainage tube in the walls of the abscess that has been laid open by rib resection or in the drainage from fistulas resulting from operation Unless the patient is treated with emetine the amebae persist in the discharge from the abscess until the latter is completely healed The habitat of the *Endamoebae* is not in the pus itself but in the walls of the abscess in the region adjoining the zone of necrosis The pus from most amebic liver abscesses is bacteriologically sterile but on occasion the abscess becomes secondarily infected and then the character of the pus changes The organisms commonly found in the aspirated pus are *Escherichia coli* and streptococci In an abscess that is secondarily infected the pus appears to lose most of its characteristic liver pus appearance It is then creamy yellowish or greenish yellow and has an odor of ordinary pus otherwise it may have a fecal odor

The differential diagnosis of amebic abscess of the liver includes primarily recognition of the presence of a disease in that area Signs and symptoms of pneumonia of the lower right lobe must be correctly evaluated These are relatively common in the course of acute amebic hepatitis with or without abscess formation and the chest and abdomen in the liver region should be given a careful examination A roentgen ray examination should be made of the chest with particular attention to the diaphragm on the right side It may be necessary to make repeated roentgen ray examinations of the chest in order to clarify the condition In addition stool examinations should be made if there is a possibility of amebic involvement Indications of fluid in the pleura or changes in the contour of the diaphragm suggest diagnostic aspiration of either the chest or the liver Other conditions to eliminate from consideration in diagnosis include subdiaphragmatic abscess which may be due to an extension of disease of the lung or pleura through the diaphragm by means of the lymphatics to perforation of a peptic ulcer and consequent discharge into the gastrohepatic ligament with subsequent involvement of the subdiaphragmatic region or to perforation of a liver abscess caused by *Escherichia coli* streptococci or staphylococci and not in any way related to amebiasis *Malaria* is commonly confused with amebic liver abscess because of the fever associated with the latter *Hepatitis* may be caused by agents other than *Endamoebae* as for example by bacterial infection due to streptococci or

staphylococci or by *Escherichia coli* Other diseases to be differentiated include phlebitis hydatid disease of the liver syphilis bilharzial disease kala azar acute and chronic gall bladder disease with or without stones appendicitis pyelitis involving the right kidney undulant fever trypanosomiasis tuberculosis and malignant growths of the liver According to Manson Bahr the golden rules in tropical practice are to think of hepatic abscess in all cases of progressive deterioration of health and to suspect it in all obscure abdominal cases associated with an evening rise of temperature and this particularly if there be an upward enlargement of or pain in the liver leukocytosis and a history of dysentery—not necessarily recent

Amebic Abscess of the Lung with Empyema

This complication is usually secondary to rupture of an amebic abscess of the liver through the diaphragm There are rare instances in which primary amebic abscess of the lung has occurred

The symptoms of primary amebic abscess of the lung are similar to those of pulmonary tuberculosis or to unresolved pneumonia with or without pleurisy or empyema Lung abscess secondary to rupture of an amebic abscess of the liver is characterized by sudden onset with or without pain Symptoms include pain in the affected lung fever chills cough and the expectoration of typical amebic pus which is chocolate colored and contains trophozoites of *E histolytica* The final diagnosis must depend on the demonstration of trophozoites of *E histolytica* in the sputum There is in addition leukocytosis the white cell count being from 15 000 to 25 000 When there is evidence of empyema aspiration should be undertaken Typical amebic pus is usually found but if the rupture of the liver abscess has been massive and large quantities of liver pus have entered the pleural cavity the material first aspirated may not contain the trophozoites of *E histolytica* This may be true of the first amebic pus expectorated by the patient at the onset of his symptoms of lung abscess following rupture of the liver abscess Treatment with emetine injections (page 23) also helps to clarify the diagnosis

Amebic Abscess of the Brain

Amebic abscess of the brain is fortunately a very rare complication of amebiasis but one which must be thought of whenever there are evidences of brain involvement in a patient who has had amebic dysentery or in whom amebiasis may be suspected Amebic hepatitis with or without abscess is a common precursor of amebic abscess of the brain

Amebic Appendicitis

Amebic appendicitis is one of the more common complications of amebiasis The symptoms are those of acute or chronic appendicitis In rare instances there are no symptoms whatever and the condition has to be diagnosed at autopsy Amebic appendicitis should be suspected in any person who com

plains of localizing symptoms during the course of acute or chronic amebic dysentery It should be considered in any patient who has a history of amebic dysentery or who has been exposed to possible infection with *E histolytica* and who currently complains of symptoms suggestive of appendicitis In all these cases careful stool examinations should be made before surgery is re sorted to unless an acute emergency arises such as evidence of perforation or abscess formation about the appendix Symptoms simulating acute or chronic appendicitis may be present in patients with intestinal amebiasis but without invasion of the appendix although in many instances the appendix is acutely involved The symptoms are caused by an acute typhlitis The correct diag nosis of amebiasis in a case that is suggestive of appendicitis is of the greatest importance because the prognosis following surgical procedures in amebic appendicitis is very poor The response to emetine and other antiamebic meas ures is prompt

Many other complications of amebiasis have been described In fact the presence of *E histolytica* in almost every organ of the body has been recorded but in many instances it is possible that there is confusion of cells of tissue origin with *E histolytica* When there is evident involvement of the genito urinary system especially in male patients the probable route of invasion is through the rectal mucosa following acute prostatitis This is most likely when a prostatic abscess has been incised through the rectum In such cases amebae may be found not only in the urine but also in the spermatic fluid

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The differential diagnosis of amebiasis depends on the type of infection involved When there are acute diarrheal symptoms the possibility of bacillary dysentery either in its acute fulminating form or in its more chronic form must be excluded (page 109) The diagnosis of amebiasis can be established most promptly by examination of freshly passed specimens of stool or bowel discharge and by the demonstration of one or more of the forms of *E histolytica* in the specimens The other protozoan infections must also be differentiated in any patient suffering from intestinal upset especially if there is diarrhea which may or may not alternate with constipation Giardial and balantidial infections are not infrequently associated with diarrhea Other conditions which are likely to cause diarrhea and other intestinal symptoms are chronic ulcerative colitis diverticulitis terminal ileitis malignant growths of the bowel lymphogranuloma venereum dietary indiscretions (particularly alco hol) and the various intestinal neuroses

PROGNOSIS

The prognosis of amebiasis varies with the age sex degree of infection of the patient and also with the presence or absence of complications

In carriers and in individuals with mild intestinal symptoms the prognosis is good as far as life and the ultimate cure of the infection are concerned In

acute amebic dysentery with proper therapy the prognosis is good for recovery from the acute symptoms but it should be guarded for the final elimination of the infection is worse with each recurrence of dysentery symptoms The danger to life is not great but many of these patients have to be watched for years and finally they must be sent away from the tropics or from any locality where reinfection is likely to occur

The prognosis for the complications of amebiasis depends on the nature of the complications the rapidity with which an accurate diagnosis is made and the mode of therapy adopted In amebic liver abscesses the prognosis is always grave but if the condition is treated promptly and efficiently the outlook is reasonably good In simple amebic hepatitis treatment with emetine is almost specific It may effect a cure even after the abscess has formed and as a result the patient need not be subjected to aspiration or to surgical intervention If there are multiple abscesses the prognosis is practically hopeless The prognosis of the complications of amebic abscess of the liver is grave If the abscess should burst the outlook will depend on the location of the rupture and the organs involved If the rupture is into the peritoneum the outlook is very poor with rupture into the lung it is better especially if the rupture is recognized early and proper therapy is instituted Many amebic abscesses of the lung remain unrecognized until the patient is so exhausted and so toxic that treatment is almost useless On the other hand if the diagnosis is made early in the disease and if treatment with emetine is instituted the prognosis is fair although it should always be guarded

Amebic appendicitis offers a good prognosis if the proper diagnosis is made and appropriate therapy is instituted If it is undiagnosed and an operation is performed the prognosis is very poor Many individuals operated on for appendicitis in the presence of intestinal amebiasis have died needlessly Early and proper recognition of the disease condition is essential for a good prognosis

The prognosis for amebic abscess of the brain is invariably hopeless

TREATMENT

Amebiasis

Treatment of amebiasis with drugs is directed toward the eradication of the parasite that causes the symptoms When the patient fails to improve after a course of therapy a careful review of the entire case should be made including stool examinations and study of the stained slides from the previous examinations to determine whether other factors are complicating the disease or whether the correct diagnosis has been made In many instances cells other than amebae have been mistaken for one of the forms of the parasite and failure of the patient to respond to treatment has led to a diagnosis of chronic amebiasis or of a type of parasite that is resistant to treatment On the other hand such conditions or complications as chronic ulcerative colitis malignant growths of the bowel bacillary dysentery lymphogranuloma venereum or diverticulitis may be present either with amebiasis or complicating it

The drugs used in the treatment of amebiasis are mainly emetine hydrochloride chiniofon (yatren quinoxyl anayodin) vioform carbarsone and bismuth subnitrate

Emetine Hydrochloride Adult dosage 0 065 gm (1 grain) by hypodermic (subcutaneous) injection given at daily intervals for a total of seven days making a total dosage of 7 grains The safest manner of giving emetine is to inject subcutaneously ½ grain twice daily It is essential to make a note of the blood pressure and pulse before the administration of each dose If any marked change should occur such as a drop in blood pressure and an increase in pulse rate the injections should be withheld and further treatment given with chiniofon (see below) The toxicity of emetine is greater than that of either chiniofon or carbarsone and it has a direct action on the heart muscle causing degenerative changes that may result in myocarditis and death It may cause diarrhea excessive muscular weakness nausea vomiting abdominal pain rapid weak pulse drop in blood pressure and fainting spells Emetine hydrochloride should be employed *only to control the symptoms of acute amebic dysentery when tropho oites of E histolytica are present* Emetine does not usually eliminate the infection it simply controls the acute dysenteric symptoms

Indications Acute amebic dysentery chronic amebiasis during acute intestinal symptoms with the passage of trophozoites of *E histolytica* the complications of amebiasis such as amebic hepatitis liver abscess lung abscess with or without empyema brain abscess appendicitis amebic typhlitis and amebic invasion of any other organs of the body

Contraindications Chronic amebiasis and in chronic amebic cyst passers or carriers when only the encysted forms of *E histolytica* are passed in the stools Emetine is contraindicated in weak and debilitated patients who show evidence of cardiac damage *Emetine should never be given by intravenous injection*

Chiniofon (yatren quinoxyl anayodin) Chemically chiniofon is sodium iodohydroxyquinoline sulfonate and contains from 26 to 28 per cent iodine on which depends the amebicidal effect of the drug

Dosage Each tablet contains 0 5 gm (4 grains) and is enteric coated The total adult dosage is 100 tablets The method of administration by mouth is 3 tablets three times daily after meals making a total daily dosage of 9 tablets This dosage is continued for eleven days until the total of 100 tablets has been taken In cases of chronic cyst passers (carriers) some physicians have given 4 tablets three times daily (12 tablets total daily dose) until the patient has taken 100 tablets If there is acute bowel irritation as in acute amebic dysentery or if patients seem sensitive to the preparation the initial dosage may be reduced and treatment started with 3 tablets daily (1 after each meal) for three days followed by 2 tablets after each meal (6 daily) this is usually well tolerated It may be necessary to administer a small dosage of powdered opium in a capsule with the chiniofon in order to reduce the bowel irritation caused by the larger doses of chiniofon Most persons do not need the powdered opium

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Vioform Used for many years as a dusting powder in surgery vioform was used to replace iodoform because it was odorless Chemically it is iodochloroxyquinoline and depends on its iodine content for its amebicidal effect The dosage of vioform is 0 25 gm (4 grains) given in capsules three times daily for ten days followed by a period of one week without therapy The same dosage of 1 capsule containing 0 5 gm (4 grains) is then given three times daily for another ten days Vioform is not as effective as chiniofon

Diodoquin Chemically diodoquin (5 7 diiodo 8 hydroxyquinoline) is a compound in which the sodium sulfonate radical of chiniofon (sodium iodohydroxyquinoline sulfonate) was replaced with a second iodine atom thus forming a double iodine compound

The dosage of diodoquin in the treatment of amebiasis depends on the severity of the infection and varies from 7 to 10 tablets daily Each tablet contains 0 1 gm (3 2 grains) It is stated that a course of treatment should continue for twenty days followed by a period of rest of from seven to ten days and then repetition of the course either with the same or increased dosage The drug is non toxic and non irritating to the bowel mucosa

Other Drugs Used in the Treatment of Amebiasis Emetine bismuth iodide treparsol Kurchi bark bismuth subnitrate dihydranol Chaparro amargoso emetine peroxide auremetine acetarsone amibarsone and gavano

Emetine bismuth iodide is a combination of bismuth emetine and iodine containing about 29 per cent emetine 1 per cent bismuth and 58 per cent iodine It is administered in capsules or enteric coated tablets The dose is 0 2 gm (3 grains) once daily for twelve days This drug causes nausea and vomiting and in addition its use may give rise to diarrhea rapid weak pulse and fall in blood pressure When these signs appear the administration of the drug must be discontinued The drug is effective as an amebicide but it has these disadvantages and no compensating advantage over chiniofon or carbarsone

Bismuth subnitrate has been used for a number of years and while its amebicidal effect is limited it has the advantage that when given in heaping teaspoonful doses at the conclusion of an attack of amebic dysentery it checks the constipation that often follows the attack and in addition patients who were formerly constipated have regular bowel function The dosage recommended is 1 teaspoonful three times daily after meals

Acute Amebic Dysentery

Treatment of acute amebic dysentery involves absolute rest in bed and injections of *emetine hydrochloride* subcutaneously in dosages not to exceed 0 065 gm (1 grain) daily for a period of from seven to nine days The blood pressure and pulse should be watched carefully before the administration of each dose If the acute condition has not subsided markedly by this time the entire case history should be reviewed to determine whether other factors are present such as bacillary dysentery malignancy and the like *Chiniofon* (anayodin quinoxyl yatren) in enteric coated tablets is given either at the

Dosages of powdered opium should not exceed 0.030 gm (1/2 grain) three times daily

Indications In acute amebic dysentery chiniofon may be given either simultaneously with or immediately following treatment with emetine in chronic intestinal amebiasis with passage of trophozoites and also encysted forms of *E histolytica* and in chronic cyst passers and carriers It is indicated also in the treatment of the complications of amebiasis * in order to rid the patient of the intestinal infection In the patients with complications chiniofon should be administered even though cysts are not found

Chiniofon is indicated in the treatment of patients with amebic dysentery in which emetine is contraindicated because of cardiac lesions In such cases it may be given by mouth in dosage of 2 pills three times daily after meals (6 pills daily) for a total of 100 pills In addition a retention enema of 200 cc of 2 per cent solution of chiniofon in warm water may be given once daily for eight to ten days A cleansing enema of sodium bicarbonate solution should be given prior to the retention enema It may be necessary to give an opiate to quiet the patient and thus facilitate retention of the medicated enema

Attention should be called to the great danger associated with giving retention enemas or any other rectal medication in cases of intestinal amebiasis or any other inflammatory condition of the bowel The bowel wall is friable the mucosa has ulcerations and the installation of any solution may cause perforation The danger is particularly great if so called high enemas are given in which the rectal tube or catheter is inserted high up into the bowel through the rectum In other instances the mere pressure of water even in amounts of 200 cc may cause perforation especially if there have been previous cleansing enemas

Carbarsone Carbarsone is an arsenical preparation and contains 28.85 per cent arsenic on which it depends for its amebicidal effect

Dosage Each capsule contains 0.25 gm (4 grains) and is administered by mouth or by enemas The dosage by mouth is 1 capsule morning and evening (2 daily) for ten days making a total of 20 capsules When given by retention enemas the quantity used is 1 per cent carbarsone in 200 cc of a 2 per cent sodium bicarbonate solution Such enemas are given once daily for five days

Indications Carbarsone acts upon the trophozoites of *E histolytica* but it is effective also against the cysts of the parasite

Carbarsone is not as effective as chiniofon and is more toxic because of its arsenic content In comparison with the other arsenical preparations it is less toxic but even with this drug manifestations of arsenical poisoning have been noted Some of these symptoms are severe abdominal pain and colic diarrhea puffiness of the face erythema skin eruptions abdominal distention prostration thready pulse and arsenical dermatitis

* So far as is known there are no toxic reactions to chiniofon the only incidental effects noted being slight bowel irritation with slight increase in bowel movements when given in full dosage Chiniofon is the most effective amebicidal drug used for elimination of cysts in amebiasis even though there are rare instances in which infections with *E histolytica* are not eliminated by a single treatment

for even the largest abscess can be successfully treated by repeated small aspirations and treatment with emetine When aspirations with the spinal puncture needle are used the degree of shock to the patient is less there is less danger of hemorrhage into the abscess cavity and the possibility is eliminated of the fistulous tract extending from the liver to the outside with its secondary infection with *E histolytica* The amount aspirated each day by use of a spinal puncture needle attached to a syringe is less than by the other methods and the aspiration takes a longer time but all these factors are in favor of the aspiration method because it causes less discomfort to the patient This method combined with emetine injections will give the highest percentage of success

Amebic Lung Abscess With or Without Empyema

Emetine injections with or without aspirations with a small needle as described for amebic liver abscess is the method of choice A course of chiniofon by mouth is also acceptable for most patients have a chronic intestinal infection as well The indications for aspiration of the lung depend on the physical signs of empyema associated with the lung abscess if these are not present it is not necessary to perform aspirations

Amebic Abscess of the Brain

If this condition is suspected immediate administration of emetine by hypodermic injections is indicated Chiniofon given by mouth is also called for

Amebic Appendicitis

When amebic appendicitis is suspected treatment must be prompt and effectively administered It calls for emetine injections and also for chiniofon by mouth *Under no circumstances should any cathartic be administered* in a suspected case of amebic appendicitis or amebic typhlitis because of the danger of development of abscess of the appendix or rupture of this organ *Surgical intervention in amebic appendicitis is contraindicated in all cases except in the gravest emergency in which there is definite evidence of abscess formation or perforation of the appendix* In such cases simple drainage through a stab wound over McBurney s point is the only surgical procedure that should be attempted and vigorous immediate therapy with emetine should be instituted

Other Complications

Treatment of other complications of amebiasis is with emetine injections carried out in the manner already outlined

DIET

The strength of the patient should be maintained There is no indication for starvation On the contrary a diet high in protein and high in vitamins with adequate starches to make up the caloric intake is of great value The

same time as emetine injections or immediately following them The dosage is 3 tablets daily for one or two days (1 after each meal) followed by 6 tablets daily for two or three days (2 after each meal) and then 9 tablets daily (3 after each meal) until the patient has taken a total of 100 tablets In selected cases carbarsone may be used but a careful watch should be maintained for evidence of toxicity

Chronic Amebiasis (Intestinal)

If the patient is passing trophozoite forms of the parasite in addition to the cysts treatment should be along the lines described for acute amebic dysentery Chiniofon is the drug of choice in chronic amebiasis

Chronic Carriers or Cyst Passers

In this form of amebic infection emetine injections are without avail they merely cause inconvenience to the patient and involve the risk of cardiac damage Treatment should be with chiniofon in the form of enteric-coated pills marketed under the trade names of chiniofon yatren anayodin or quinoxyl If an arsenical preparation is preferred carbarsone is the drug of choice Chiniofon is the most effective drug used in the elimination of the cysts of *E histolytica* and even though in a few instances there may be colicky abdominal or mild diarrheal pains during the period of administration no toxic effects have been observed by numerous physicians who have used it and the elimination of cysts is almost certain with this drug The editor agrees with Colonel Craig and numerous others including the late F W O Connor that extended experience with chiniofon proves that it is the most effective drug we possess in the treatment of infection with *E histolytica* although there are some instances in which infections are not eliminated completely with a single course of therapy especially if they are chronic and of long standing Carbarsone is less effective and more toxic than chiniofon although of the arsenical group of drugs it is the least toxic of the preparations available Chiniofon is the drug of choice

Amebic Hepatitis

Before the development of an amebic liver abscess injections of emetine are almost specific and in some instances may even be considered as of therapeutic diagnostic value If cysts are present in the stools they should be eliminated

Amebic Liver Abscess

Emetine injections which are specific and aspiration of the abscess with a spinal puncture needle are the methods of choice A course of therapy with chiniofon may be given by mouth to eliminate any cysts which might be present in the stools even though these may not have been found on stool examinations Aspiration with a spinal puncture needle attached to a 20 cc or a 30 cc. syringe is preferable to open operation or aspiration with a large trochar Open operation or the insertion of a large trochar is rarely necessary

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dietary outlined under bacillary dysentery or under typhoid fever is acceptable in amebiasis

SUPPLEMENTARY THERAPY

In addition to the specific therapy in amebiasis the patient is aided in his recovery by the addition of liver extract injections (crude liver extract) in amounts of from 3 to 5 cc every other day given intramuscularly preferably into the buttocks The use of vitamin B complex and vitamin C both in the dietary and also in crystalline form is most acceptable When they are indicated blood transfusions plasma transfusions and glucose infusions may be given to the patient as outlined under the treatment of bacillary dysentery (page 114)

PROPHYLAXIS

Craig has suggested that diodoquin may be of value as a prophylactic agent against amebic dysentery In his opinion 7 tablets daily for twenty days as used in the treatment of chronic amebiasis should afford adequate protection against infection with amebae such as would come through food or drink during the period of administration

It has been the habit of some travelers in the tropics to take from 1 to 3 tablets of chiniofon daily at the onset of an attack of diarrhea and continue with this dosage as long as clinical symptoms persist The editor has examined a number of these persons and found them free from amebae

The use of either diodoquin or chiniofon should be encouraged under these conditions There is no contraindication to the use of either of these drugs in the dosage mentioned or because of their iodine content under the conditions suggested It may be that these drugs will prove of value against both amebic and bacillary dysentery

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DIAGNOSTIC METHODS

Methods for Obtaining Specimens

(1) *Dosage with Epsom salts* The patient should be instructed to take a dose of Epsom salts that will produce a mushy but not watery movement and to come to the physician s office or laboratory for evacuation of the stool All mucus and stools passed should be examined immediately after they are passed and smears made for immediate fixation in Schaudinn s fluid

(2) *Colonic irrigation* A colonic irrigation with tepid normal saline is continued until the return flow is entirely clear of fecal matter The terminal mucus should be examined immediately The best specimens are those the patient passes after the irrigation is completed

(3) *Normal saline enemas* The patient is given a series of three tepid normal saline enemas The discharge following the first two may be discarded but that following the third should be kept for examination This procedure can be carried out either at home or at the physician s office In the former case the patient should be instructed to retain some of the final enema and not to evacuate it until he reaches the physician s office

Amebae and Cellular Exudates

Even though cellular exudates may be present in these specimens amebae can be visualized readily and identified Freshly passed trophozoite forms exhibit all their characteristics In Lugol s solution the details of nuclear structure of the cysts of amebae can be distinguished without difficulty If a specimen is stained with Loffler s methylene blue or brilliant cresyl blue all cells except the amebae will absorb the stain immediately This technique removes the danger of confusing cells with amebae although it must be borne in mind that after a time the amebae will also take up the stain

Routine Technique

In the diagnosis of amebiasis it is of first importance that specimens should be prepared and examined as soon as possible after they have been passed Many amebae degenerate so rapidly after they have left the body that it becomes exceedingly difficult if not impossible to identify them The trophozoites of *E histolytica* will not usually remain motile even in the incubator for more than from thirty to forty minutes after they have been passed neither do they retain their characteristic form Hence it is particularly desirable to follow a routine technique in the preparation of specimens for microscopic examination in order to avoid risk of confusion in the diagnosis of amebiasis This technique involves the preparation for five types of smear

(1) *A saline smear* unstained in which the movements of trophozoites and also the size and shape of cysts can be observed This smear is made by emulsifying a small bit of the fecal mass in a drop of normal saline with an applicator on a glass slide As a rule smears should be made from several portions of the specimen If bits of mucus adhere to the mass these should be removed with

CHAPTER III

CLINICAL LABORATORY METHODS IN INTESTINAL PROTOZOA

Z T BERCOVITZ

THE PROTOZOA WHICH INVADE THE GASTRO-INTESTINAL tract of man are unicellular organisms Some of them such as *Endamoeba histolytica* are definitely related to pathologic changes in the human intestine while others such as *Endamoeba coli* do not seem to give rise to harmful effects Many different kinds of protozoa invade the human intestinal tract The following is a brief description of those which are encountered most frequently

Endamoeba histolytica causes amebic dysentery and consequently belongs to the class of protozoa that are pathogenic to man There are three stages in its life cycle the trophozoite precystic and encysted (cyst) forms It has a typical nuclear structure by which it can be identified

Endamoeba coli is frequently found in intestinal discharges although there is no evidence to show that it is pathogenic to man It can be identified by its morphologic characteristics and also by its nucleus

Iodamoeba butschlii which Wenyon termed at first iodine cysts because of the presence of large glycogen masses which absorb the iodine of Lugol s solution

Dientamoeba fragilis is present in bowel discharges but is missed very often because of the rapidity with which it degenerates after leaving its host

Endolimax nana is a relatively common intestinal protozoan It can be identified readily by its nuclear structure

Giardia lamblia is a flagellate which can be recognized by its characteristic shape axostyles flagella and nuclei

Chilomastix mesnili is also a flagellate which can be recognized without difficulty

Trichomonas hominis occurs occasionally in stools

Balantidium coli is the largest protozoan that invades the human intestinal tract It can be recognized by its size and also by its cilia It is pathogenic to man

Isospora hominis occurs rarely in stools and is the only member of that group to invade man

(c) Small funnel

(d) Small glass receptacle

(e) Glass stirring rod

(f) Gauze

II *Procedure*

(a) Emulsify carefully a fecal mass about the size of an almond in about 10 cc of tepid tap water

(b) When all the fecal mass is broken up pour it through a double layer of gauze in a glass funnel into the Wassermann tube

(c) Centrifuge at high speed from forty five seconds to one minute

(d) Decant the supernatant cloudy fluid and add fresh tepid water

(e) Emulsify carefully the sediment so that it is equally distributed throughout the tube

(f) Centrifuge again at high speed for from forty five seconds to one minute

(g) Repeat this procedure until the supernatant liquid is clear This will require three or four washings

(h) Add a small amount of zinc sulphate to the sediment in the bottom of the tube and emulsify carefully Add the zinc sulphate solution until it reaches within one half inch of the top of the tube but be *particularly careful not to allow the solution to reach the rim of the tube* because the cysts float very readily and may be lost Centrifuge for forty five seconds

(i) Remove several loopfuls from the surface of the zinc sulphate solution with a bacteriological loop and place them on a coverslip

(j) Emulsify this carefully with a drop of D Antoni s iodine solution or with Lugol s solution The former is better adapted for use with the concentration technique An emulsion should be made both in saline and in iodine

Appearance of Protozoa in Unstained Saline Smears (Plate I fig 1)

In unstained saline smears the protozoa stand out as small refractile bodies When studied under the high dry objective these are seen to have cellular contents and when studied under the oil immersion objective some of these contents can be distinguished The nuclei of some encysted forms are not readily seen especially those of *E histolytica* cysts The nuclei of some other amebae however can be seen in the unstained saline preparation This is particularly true of the nuclei of *E coli* which can be visualized readily in the saline preparation This point serves to distinguish the cysts of *E coli* from those of *E histolytica* Chromatoid bodies when present are usually visible in the saline preparation In the case of *G lamblia* the axostyles and flagella can be seen in the saline smear

Some trophozoites can be distinguished by a characteristic motility This motility can be observed in the saline smear Thus in the case of *E histolytica* the progressive motility of the freshly passed specimen can be observed and also the formation of pseudopodia with the typical separation of ectoplasm and endoplasm

the applicator and emulsified on a glass slide in a drop of saline This emulsion should if possible be kept warm during microscopic examination

(2) *A smear made with Lugol s solution* in which it is possible to examine the nuclear structure of the cysts of amebae Lugol s solution should be substituted for the drop of normal saline in the preparation of this smear

(3) *Loffler s methylene blue* is of particular value when there are numerous cells as well as amebae present To make this smear put a drop of Loffler s methylene blue on a clean glass slide and emulsify in it a drop of the bowel discharge Then cover the emulsion with a coverslip *Do not allow to dry*

(4) *Brilliant cresyl blue* A drop of 1 per cent aqueous solution is used in the same manner as Loffler s methylene blue It enables better cytologic differentiation to be made

(5) *A wet smear fixed in Schaudinn s* solution and stained with Heidenhain s iron hematoxylin technique This smear should be used whenever it is suspected that protozoa are present It is of special value also for permanent record and should therefore be kept for study and for subsequent review of the case

Importance of Repeated Examinations

Repeated examinations of several specimens are necessary if errors in diagnosis are to be reduced to a minimum For this purpose a specimen should be obtained every day or every other day for at least six days Otherwise the patient should be given Epsom salts and several specimens should be examined as soon as possible on the same day that they are passed Even with the use of the more recently developed concentration techniques it has been found necessary to examine numerous specimens passed on different days

Concentration Technique

Faust s concentration technique is particularly valuable because it enables the technician to find the cysts of protozoa when only a few of these are present in the specimen *It is possible to see them unobstructed by the presence of* fecal matter As a result many specimens are now found to contain cysts which previously were considered negative a fact which makes it important to make a concentration of every specimen to be examined Faust s method does not affect the viability of cysts present in the specimen and it gives a concentration possibly as high as one thousand fold The method depends upon centrifugal flotation with zinc sulphate specific gravity 1 180 as the levitating medium For successful concentration the specific gravity of the zinc sulphate solution is of very great importance *It is also important to see that the final washing* does not reach the top of the glass tube

ZINC SULPHATE CENTRIFUGAL FLOTATION METHOD (FAUST)

I *Materials*

(*a*) Zinc sulphate solution specific gravity 1 180 can be obtained by making up a 33 per cent solution

(*b*) Wassermann tubes (1/ inch in diameter)

(c) Mordant 2 per cent to 4 per cent iron alum at 30 C. for 10 minutes (short 2 min)
(d) Wash well in running water for 5 minutes
(e) Stain in 0 5 per cent Heidenhain s hematoxylin at 30 C for 30 minutes (short 2 min)
(f) Wash well in running water for 5 minutes
(g) Decolorize in 2 per cent to 4 per cent iron alum
Watch under microscope until nuclei are clearly visible
(h) Wash well in running water for 5 minutes
(i) Immerse successively in
50 per cent alcohol for 2 minutes
70 per cent alcohol for 2 minutes
85 per cent alcohol for 2 minutes
95 per cent alcohol for 5 minutes
Absolute alcohol for 5 minutes
Absolute alcohol plus xylol for 5 minutes
Xylol for 5 minutes
(j) Heat add Canada balsam and mount

INDIRECT METHODS OF DIAGNOSIS

(1) *Charcot Leyden Crystals* The presence of Charcot Leyden crystals in the stools is of diagnostic importance because it indicates a parasitic infection of the bowel These crystals occur frequently in the stools of patients suffering from amebic dysentery consequently when they are found in specimens a careful search should be made for typical forms of *E histolytica*

Charcot Leyden crystals are highly refractile and clear in the freshly passed stool The crystals are faint greenish in color They vary in size from 3 to 6 microns In shape whetstone is constant although fragments of broken crystals may be found

Charcot Leyden crystals dissolve readily in hydrochloric acid a quality which serves to distinguish them from fatty acid crystals which may be con fused with them

(2) *Complement Fixation Test* The complement fixation test is one of the most valuable advances made recently in diagnostic methods for determining the presence of *E histolytica* Craig who developed the test found that it was highly specific for infection and that it gave a positive result in about 90 per cent of cases He also found that the reaction to it became negative after the infection had been eliminated The complement fixation test he stated should not be employed except as a check upon the results when it is possible to have the stools examined for amoebae Although the complement fixation test gives promise of being routinely reliable for amebiasis it does not at the present time replace the time-consuming painstaking careful search of speci mens of the stools for the various forms of amebae Craig has given the details of his technique in a monograph entitled Amebiasis and Amebic Dysentery As the complement fixation test calls for the services of an experienced serologist it should not be used by others

Appearance of Protozoa in Iodine Smears (Plate I fig 2)

Lugol s solution or D Antonni s iodine is used for smears In these smears the nuclei of the cysts of amebae become prominent and can be more readily and more definitely recognized than in the saline smears

Under these conditions cysts stand out as clearly defined walnut brown bodies and by careful focusing it is usually possible to study their nuclear detail With the Faust technique it is possible to examine the cysts while they are clear from fecal matter This is of particular value in the identification of nuclear structures Chromatoid bodies cannot be seen in the iodine smear but a glycogen mass if present absorbs iodine and appears as a dark brown mass

Appearance of Protozoa in Fixed Stained Preparations (Plate I fig 3)

Heidenhain s iron hematoxylin method is usually employed for fixing and staining specimens so that they will be available for careful and detailed examination and also for permanent record The background in these specimens is usually light blue or brown Cysts can be recognized by the clear halos which surround them setting them off from the surrounding fecal mass With the oil immersion it is possible to recognize the ectoplasm and also the cytoplasm of the cyst The details of the nuclear structure can be distinguished Inclusions such as chromatoid bodies or red blood corpuscles if present stain a deep blue and can be recognized by their typical structure The glycogen vacuoles in *Iodamoebae* are clear while the axonemes in flagellates have the appearance of dark bodies rod shaped or blunt curved or straight in form

Heidenhain s Iron Hematoxylin Technique

I A freshly prepared smear of the specimen should be fixed in Schaudinn s solution and stained while wet according to the accepted technique Because the specimen will be ruined if it is allowed to dry it is of first importance that it should be kept moist throughout the entire process of staining When the fixed stained specimen is prepared with precision it will be found possible to study all the structures present including the nuclei

II *Staining Technique*

Schaudinn s Solution (Fixation)

2 parts of saturated mercuric chloride solution
1 part absolute alcohol
5 cc glacial acetic acid added to 100 cc of the above mixture
[Note Prepare fresh each day before use]

Staining Method

(a) Schaudinn s solution—fixation from fifteen to twenty minutes heated to 60 C

(b) Rinse in 50 per cent alcohol then immerse successively into
70 per cent alcohol iodine for 2 minutes
70 per cent alcohol for 2 minutes
50 per cent alcohol for 2 minutes
Rinse in water

Cultivation of Intestinal Protozoa

Intestinal protozoa were first cultivated by Cutler in 1918 but credit is usually given to Boeck and Drbohlav who in 1924–1925 were able to maintain cultures for an indefinite period of time Their findings have been confirmed by subsequent investigators and various types of media have been worked out These media are all satisfactory in the hands of experienced workers For ordinary laboratory work it is on the whole more desirable to become experienced with one medium and to use it almost exclusively rather than to use several media with which the worker is less familiar The most commonly used media for the cultivation of *E histolytica* and other parasitic amebae are Craig s Locke serum medium St John s medium Boeck and Drbohlav s Locke egg serum medium the Locke egg albumen medium and Tsuchiya s medium

The work of culturing *E histolytica* is intensely fascinating and has great value in that as the technique for culturing this protozoan is developed it may lead to advancement in other lines of work especially in connection with the complement fixation reaction As a diagnostic method the culture is interesting but it has not yet taken the place of the careful microscopic examination of freshly passed stools for the various forms of this parasite

The details of culture media and methods have been given by Craig Craig and Faust Stitt (Strong s revision) and Manson Bahr

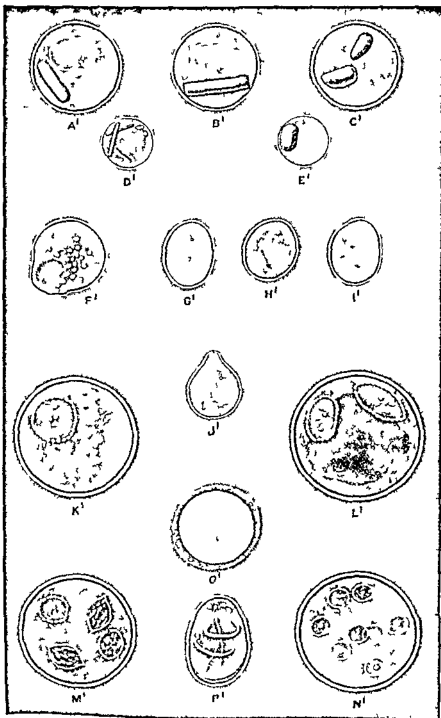


PLATE I Figure 1

PLATE I FIGURE 1

CYSTS OF INTESTINAL PROTOZOA

Cysts of intestinal protozoa as they appear alive and unstained in saline smears Semi diagrammatic figures Magnification × 2000

A B[1] C[1] D[1] E[1] Cysts of *Endamoeba histolytica*

F[1] Mature cyst of *Iodamoeba butschlii*

G[1] H[1] I[1] Cysts of *Endolimax nana*

J[1] Cyst of *Chilomastix mesnili*

K[1] L[1] M[1] N[1] Cysts of *Endamoeba coli*

O[1] *Blastocystis hominis*

P Cyst of *Giardia lamblia* (*intestinalis*)

(From Dobell and O Connor The Intestinal Protozoa of Man John Bale Sons & Danielsson)

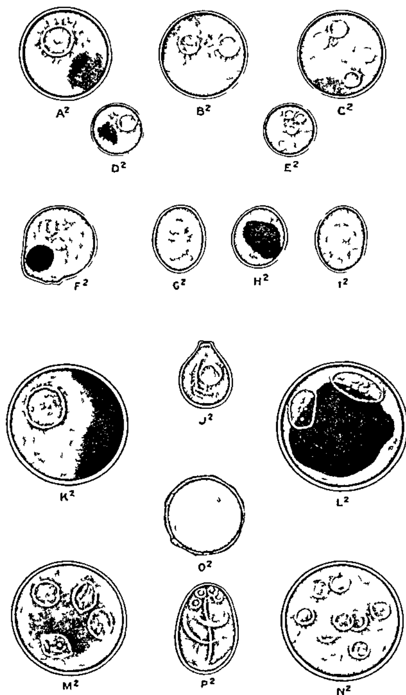


PLATE I Figure

PLATE I FIGURE .

CYSTS OF INTESTINAL PROTOZOA

Cysts of intestinal protozoa as they appear in the iodine solution Semi-diagrammatic figures Magnification × 000

A B C D E Cysts of *Endamoeba histolytica*

F Mature cyst of *Iodamoeba butschlii*

G H I Cysts of *Endolimax nana*

J Cyst of *Chilomastix mesnili*

K L M² N Cysts of *Endamoeba coli*

O *Blastocystis hominis*

P Cyst of *Giardia lamblia* (*intestinalis*)

(From Dobell and O Connor The Intestinal Protozoa of Man John Bale Sons & Danielsson)

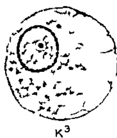














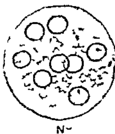



PLATE I Figure 3

PLATE I FIGURE 3

CYSTS OF INTESTINAL PROTOZOA

Cysts of intestinal protozoa as they appear when stained with iron hematoxylin (Compare with Plate I figures 1 and 2)

A^3 B^3 C^3 D^3 E Cysts of *Endamoeba histolytica*

F^3 Mature cyst of *Iodamoeba butschlii*

G^3 H I^3 Cysts of *Endolimax nana*

J^3 Cyst of *Chilomastix mesnili*

K^3 L^3 M^3 N^3 Cysts of *Endamoeba coli*

O *Plastocystis hominis*

P^3 Cyst of *Giardia lamblia* (*intestinalis*)

(From Dobell and O Connor The Intestinal Protozoa of Man John Bale Sons & Danielsson)

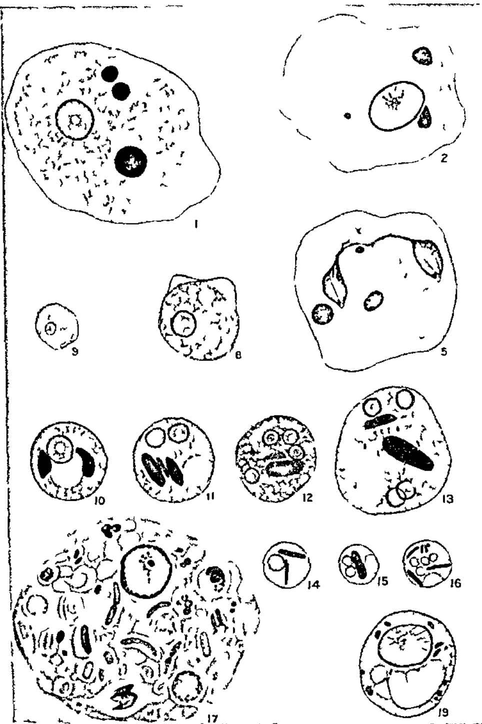


PLATE II FIGURE 1

PLATE II Figure 1

Endamoeba histolytica

1 Active large form containing three red blood corpuscles From stool of a case of amebic dysentery (Stained with Weigert s iron hematoxylin and eosin)

2 Successive stages in division From specimens in sections of ulcers in large intestine of experimentally infected kitten (Fixed in Bouin s fluid and stained in various ways)

3 4 5 6 7 (See also Plate II fig 2) Successive stages in division

8 9 Precystic amebae belonging to strains forming large and small cysts respectively (Number 8 Mann s stain Number 9 haemalum)

10 11 12 Uninucleate binucleate and quadrinucleate cysts respectively from same case as No 8 Strain forming cysts with mean diameter of 13 5 microns (Mann s stain)

13 Quadrinucleate cyst belonging to a strain with cysts measuring 15 microns in average diameter (Haemalum)

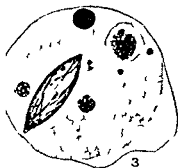
14 15 16 Uninucleate binucleate and quadrinucleate cysts respectively—belonging to a strain producing cysts with an average diameter of 6 6 microns (Haemalum)

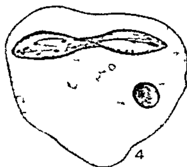
17 *Endamoeba coli* Large active ameba from human stool (Heidenhain s iron hematoxylin and eosin)

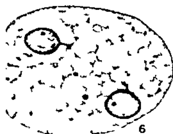
19 *Endamoeba coli* cyst

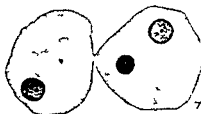
All drawings from fixed stained specimens Magnification × 2000 (From Dobell and O Connor The Intestinal Protozoa of Man John Bale Sons & Danielsson)

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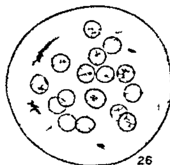




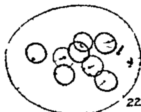
















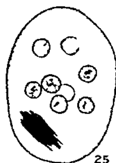


PLATE II Figure •

PLATE II Figure 2

Endamoeba histolytica

3 4 6 , Successive stages in division (See also Plate II fig 1)

Endamoeba coli

1, (See Plate II fig 1)

18 Precystic ameba Note small size and freedom from food inclusions (Mann s stain)

o- Successive stages in development of cysts which contain 2 4 and 8 nuclei respectively (No 20 Mann s stain No 1 Bouin s fluid and alcoholic ferric chloride iron haematein No 2 Heidenhain s iron hematoxylin)

23 Very small 8 nucleate cyst of *E coli* (Haemalum and eosin)

4 8 nucleate cyst containing filamentar chromatoid bodies (Haemalum)

5 8 nucleate cyst containing a sheaf of spicular chromatoids (Haemalum)

6 Very large cyst containing 16 nuclei (Haemalum)

All drawings from fixed stained specimens Magnification × 2000 (From Dobell and O Connor The Intestinal Protozoa of Man John Bale Sons & Danielsson)

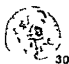












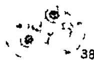




















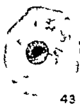








PLATE III

PLATE III

Intestinal Amebae

Endolimax nana

27 30 Four ordinary individuals showing various common types of nuclear structure

31 32 Two individuals parasitized by *Sphaerita* (No 32 stained haemalum)

33 34 35 Three successive stages in development of cysts containing 1 2 and 4 nuclei respectively

36 Mature 4 nucleate cyst containing filamentar and granular inclusions

37 Supernucleate cyst containing 8 nuclei (Haemalum)

Dientamoeba fragilis

38 39 Two ordinary binucleate individuals

40 A uninucleate specimen

Iodamoeba butschlii

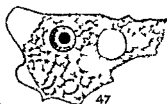
41 42 Two ordinary ameboid individuals

43 Precystic ameba

44 An organism just encysting

45 46 Typical cysts—No 46 a very irregular specimen such as is commonly seen in this species (Haemalum and eosin)

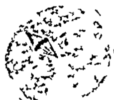
All drawings from fixed stained specimens Magnification × 2000 (From Dobell and O Connor The Intestinal Protozoa of Man John Bale Sons & Danielsson)





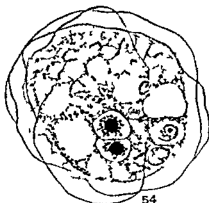












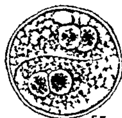


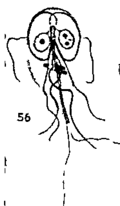
PLATE IV

PLATE IV

COPROZOIC AMEBAE FROM HUMAN FECES

47 *Dimastigamoeba gruberi* ameboid form
48 *D gruberi* free swimming flagellate form
49 Stage in division (equatorial plate) of ameboid form of *D gruberi*
50 Cyst of *D gruberi*
51 *Hartmannella hyalina* ordinary ameba
52 Stage in division (equatorial plate) of *H hyalina*
53 Cyst of *H hyalina*
54 *Sappinia diploidea* ordinary individual (Note the two large nuclei in apposition)
55 Newly formed cyst of *S diploidea* containing two individuals

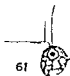
All drawings from fixed stained specimens Magnification × 2000 (From Dobell and O Connor The Intestinal Protozoa of Man John Bale Sons & Danielsson)


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PLATE V

PLATE V

Intestinal Flagellates

Giardia intestinalis (Fixation Bouin s fluid)

56 Active flagellate ventral view

57 Similar flagellate in profile (ventral surface to right dorsal to left of figure)

58 Binucleate cyst

59 Quadrinucleate cyst—later stage of development

Enteromonas hominis

60 Active flagellate typical form with 4 flagella—3 free and 1 recurrent and adherent to the body (*Tricercomonas* of Wenyon and O Connor)

61 Form in which the recurrent flagellum is not clearly visible (*Enteromonas* of Fonseca)

62 Form in which only anterior flagella are visible (*Diplocercomonas* of Chalmers and Pekkola)

63 Typical form showing 2 blepharoplasts

64–66 Uninucleate binucleate and quadrinucleate (mature) cysts respectively

Trichomonas hominis

67 Small individual with 3 anterior flagella

68 *Large individual with 3 anterior flagella (Tritrichomonas ?)*

69 Individual with 4 anterior flagella (*Tetratrichomonas* ?)

Embadomonas intestinalis

70 Active flagellate

71 Cyst

Chilomastix mesnili

72 Active flagellate ventral view

73 Smaller individual from right side

74 Individual seen anteroventrally—to show the arrangement of blepharoplasts and organs arising from them

75 Mature cyst (Fixation Bouin s fluid)

All drawings from fixed stained specimens Magnification $\times$ 2000 (From Dobell and O Connor The Intestinal Protozoa of Man John Bale Sons & Danielsson)

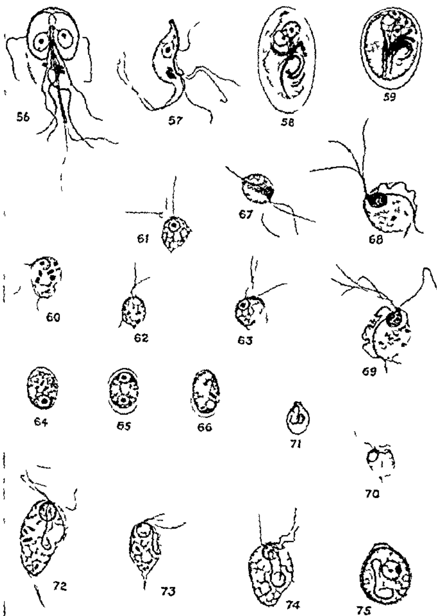


PLATE V

PLATE VI

COPROZOIC FLAGELLATES FROM HUMAN FECES

Bodo caudatus

76 Living organism—unstained
77 78 *Stained specimens* (Fixation alcoholic picro acetic)
79 Cyst stained specimen

Bodo edax

80 Active flagellate

Cercomonas longicauda

81 Living flagellate creeping Unstained
8 Stained specimen
83 Cyst—living and unstained

Cercomonas crassicauda

84 85 Active flagellates (stained alcoholic iron haematein)
86 Cyst (stained as preceding)

Helkesimastix faecicola

87 88 Two flagellates

Copromonas subtilis

89 *Ordinary flagellate*
90 Dwarf form from culture
91 Stage in longitudinal division
9 Early stage of conjugation
93 Cyst

Chlamydophrys stercorea

94 An individual from the feces of a toad (The filose pseudopodia projecting through the shell opening are contracted as a result of fixation with formalin)

All drawings from fixed stained specimens Magnification × 000 (From Dobell and O Connor The Intestinal Protozoa of Man John Bale Sons & Danielsson)

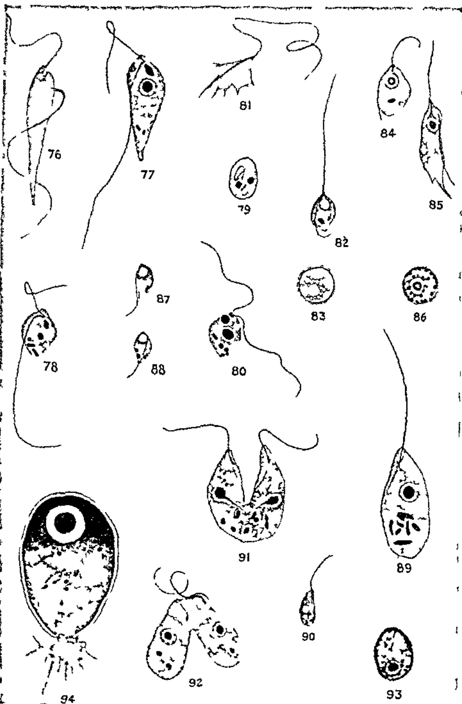


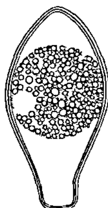
PLATE VI

PLATE VII

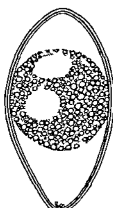
Isospora hominis

95 Oocyst with unsegmented protoplasm as usually passed in stools
96 Later stage nucleus divided into two
97 Later stage protoplasm segmented into two sporoblasts
98 Fully developed oocyst containing two spores—each containing four sporozoites
99 Degenerate oocyst which has failed to develop

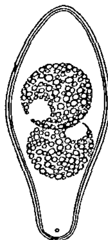
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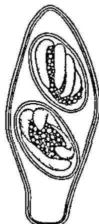
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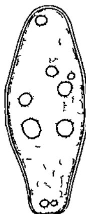
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PLATE VII

PLATE VIII

OOCYSTS OF *Isospora hominis* AND *Eimeria* SPECIES

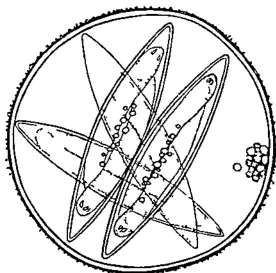
100 Degenerate oocyst of *Isospora hominis* which has failed to develop

101 *Eimeria oxyspora* A ripe oocyst containing four fully formed spores

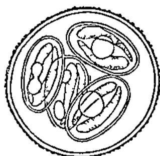
102 *Eimeria wenyoni* A ripe oocyst containing four fully formed spores (After Wenyon 1915)

103 *Eimeria snijdersi* Ripe oocyst with four fully developed spores (Combined from figures and specimens of Dr E P Snijders)

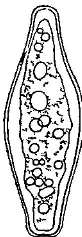
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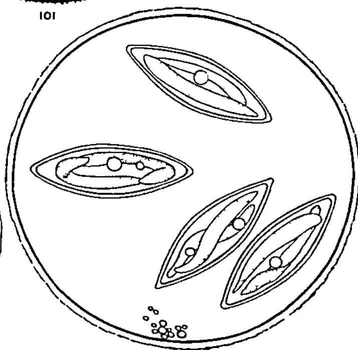
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PLATE VIII

PLATE IX

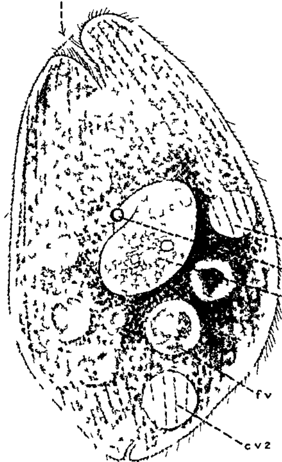
Balantidium coli

104 *Balantidium coli* (× 2000) Active ciliate semidiagrammatic Living specimen seen from left side *N* meganucleus *n* micronucleus *cv 1* anterior contractile vacuole *cv 2* posterior contractile vacuole *fv* food vacuole *mo* mouth

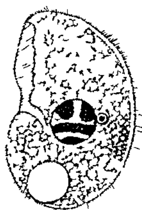
105 *Balantidium minutum* × 2000

106 *Nyctotherus faba* × 2000

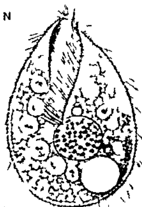
(From Dobell and O Connor The Intestinal Protozoa of Man John Bale Sons & Danielsson)



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PLATE IX

PLATE X

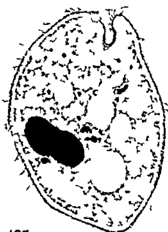
Balantidium coli

107 *Balantidium coli* (× 1000) Specimen from stool of a human case of balantidiasis Fixed sublimate alcohol stained Heidenhain s iron hematoxylin

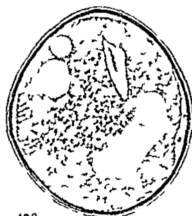
108 *Balantidium coli* Cyst × 1000 Living from feces of pig

109 Part of the periphery of a balantidial ulcer colon of human case of balantidiasis

(From Dobell and O Connor The Intestinal Protozoa of Man John Bale Sons & Danielsson)



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PLATE X

PLATE X

Balantidium coli

107 *Balantidium coli* (× 1000) Specimen from stool of a human case of balantidiasis Fixed sublimate alcohol stained Heidenhain s iron hematoxylin

108 *Balantidium coli* Cyst × 1000 Living from feces of pig

109 Part of the periphery of a balantidial ulcer colon of human case of balantidiasis

(From Dobell and O Connor The Intestinal Protozoa of Man John Bale Sons & Danielsson)

while those of the small strains may be only 15 microns in diameter

Shape This ameba is variable in shape it changes constantly when active through the formation of finger like pseudopodia but becomes rounded when inactive and when it dies

Ectoplasm The ectoplasm which is the outer covering of the ameba has the appearance of a clear glassy halo enveloping the parasite It is clearly separated from the endoplasm When freshly passed the parasites move rapidly in sluglike fashion and there is no noticeable differentiation between ectoplasm and endoplasm But when the feces have cooled they become less active and develop the characteristic pseudopodia composed of ectoplasm which are manifestly distinct from the endoplasm

Endoplasm (cytoplasm) The endoplasm of *E histolytica* is finely granular and has the appearance of colorless ground glass It may contain red blood corpuscles and if these are present it can be concluded with almost complete certainty that the ameba is *E histolytica* Unlike many other intestinal protozoa *E histolytica* does not ingest bacteria although following the death of the parasite bacteria may invade it As well as red blood corpuscles the endoplasm of *E histolytica* may contain food vacuoles In freshly passed amebae however bacteria and vacuoles are both absent and the cytoplasm is both clear and free from inclusions Although the nucleus is not as a rule visible in the freshly passed amebae it may sometimes be seen very faintly within the endoplasm some minutes after it is out of the body It is annular in form and is composed of refractive granules In order to observe these characteristics the investigator must examine the ameba within thirty to forty minutes after it has been passed because it disintegrates rapidly

Motility Motility of *E histolytica* must be studied in the freshly passed specimen Within a very brief period of time the motile forms of *E histolytica* not only tend to become rounded out and non motile but also to degenerate and disappear from the mucus A healthy active ameba when freshly passed is very active and moves rapidly (Fig 7A) Its movement is sluglike and the appearance of the ameba at this stage has been described as ribbon or tape like as it makes its way through the mucus In this form the outline of the ameba with its round glass like cytoplasm only can be seen The ectoplasm appears as a white refractile line and is readily visualized The nuclear structure is not visible Ingested erythrocytes are often found in these forms if the stool contains blood After a few minutes (Fig 7B) the exceedingly rapid sluglike movement of the ameba gives way to deliberate but still active motility with pseudopodia At this stage which is the one more commonly seen the pseudopodia are clear hyaline finger like projections that extrude in an explosive manner and that are distinctly differentiated from the rest of the cytoplasm A few moments later the cytoplasm seems to flow into the pseudopodia and in this manner the ameba moves forward If the ameba has ingested red blood corpuscles (Fig 7C) they can be seen readily in the freshly passed and unstained parasite and appear as circular bodies of a different density from the cytoplasm of the ameba and of a yellowish green color During active

CHAPTER IV

DESCRIPTION OF THE INTESTINAL PROTOZOA

Z T BERCOVITZ

ENDAMOEBA HISTOLYTICA

ENDAMOEBA HISTOLYTICA THE COMMONEST PROTOZOAN pathogenic to man is an ameba that multiplies by simple division and is characterized by trophozoite precystic and encysted stages of life and by the existence of several strains which differ in size only

The *trophozoites* of *E histolytica* can be recognized and distinguished from all other protozoa by (1) *the progressive motility of the ameba with the* formation of active finger like pseudopodia which extrude in an explosive manner (2) the ingestion of red blood corpuscles but not of bacteria (3) the clear differentiation of endoplasm and ectoplasm and also by (4) the central karyosome together with its halo within the clear zone of the nucleus *and the delicate uniform nuclear beading*

The *precystic forms* intermediate in size between the trophozoites and the cysts are rounded free from inclusions and sluggish in movement The single nucleus of the precyst has the same structure as that of the trophozoite

The *encysted forms* which appear when a smooth transparent wall is formed around the precyst are typically spherical and contain when *fully* developed four nuclei which have exactly the same structure as the nuclei of the free forms Chromatoid bars are frequently present in the cytoplasm of the cysts

The *habitat* of *E histolytica* is the mucous submucous and sometimes also the muscular layers of the large intestine It is found in blood stained mucus in acute dysentery and in mucus passed following saline laxatives saline enemas and colonic irrigations The liver is the most usual site of secondary infection but the parasite also invades the lung brain spleen and other tissues The trophozoite form only is found in the site of secondary infection

Trophozoite Forms (Plate II)

Size The average size of the trophozoites of *E histolytica* is from 18 to 30 microns in diameter The trophozoites of large strains may measure 60 microns

motility the red blood corpuscles may be seen tumbling about within the body of the parasite A few minutes later the ameba begins to lose its active motility Motility is still progressive but is definitely slower It has a single pseudo podium which is relatively large and well defined and shows marked separa tion of ectoplasm and endoplasm At this time about twenty to thirty minutes after being passed the first faint suggestion of the nucleus can be observed About ten minutes later the ameba is beginning to become rounded and its nucleus is also faintly visible From this time onward the parasite ceases to exhibit motility

Nucleus The nuclear structure of the *E histolytica* trophozoite can be sat isfactorily studied only in freshly passed ameba In unstained preparations the nucleus of the parasite is not usually visible but in stained preparations it can be observed as a vesicular open ring about 4 to 7 microns in diameter lined with very delicate granules or beads of chromatin matter and sepa rated from the endoplasm by the nuclear membrane This membrane is color less and very delicate in texture The chromatin granules which line the nuclear membrane appear to be uniform in size and in close contact with each other Within a clear zone in the center of the nucleus is the karyosome which is a small very fine dot of chromatin matter The karyosome is surrounded by a halo of achromatic matter and this like the position of the karyosome in the nucleus is a distinguishing characteristic of *E histolytica*

Precystic Forms

Precystic forms (Plate II) represent the phase of development of the ameba prior to encystation At this stage it loses its active motility and becomes sluggish It eliminates red blood corpuscles and tissue inclusions divides and becomes reduced in size

Location The trophozoites pass from the intestinal tissues to the lumen of the bowel where division and the elimination of red blood corpuscles and other inclusions take place resulting in the formation of the precystic forms

Size The precystic forms are intermediate in size between the trophozoites and the cysts Their size depends on their strain

Shape At this stage the ameba becomes rounded or slightly oval and may extrude short blunt pseudopodia which do not exhibit the activity of the pseudopodia in the trophozoite stage

Motility If present at all movement is sluggish it is not definitely progres sive as in the trophozoite form

Ectoplasm The differentiation between ectoplasm and endoplasm is slight although there may be slight pseudopoid formation

Endoplasm The endoplasm is hyaline it may have a glycogen mass and chromatoid bodies It has no tissue or red blood corpuscle inclusions

Nucleus The nucleus of the precystic form is similar to those of the tropho zoites It is single but the details of the nuclear structure must be brought out by staining It has the appearance of a ring of refractive granules the chromatin of which may be slightly thicker than in the trophozoite form The karyosome

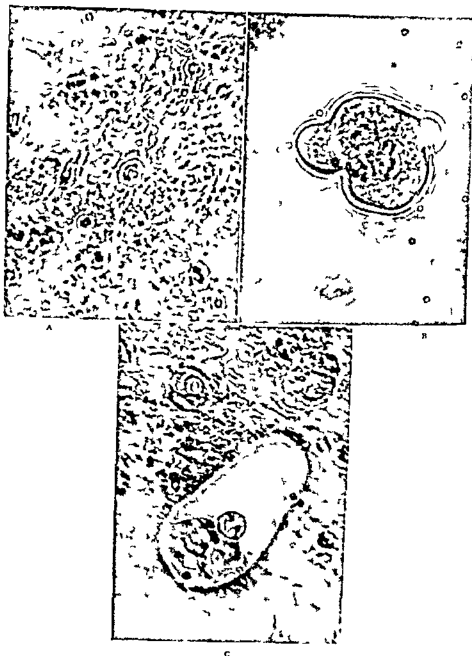


Fig 7 *Endamoeba histolytica* trophozoites freshly passed unstained in normal saline showing types of motility A Very rapid sluglike motility (ribbon or tapelike) B The same parasite a few minutes later showing pseudopodia separation of ectoplasm from endoplasm no nucleus visible C Another parasite on the same slide showing ingested red blood cell as a circular body of different density from the cytoplasm Oil immersion × 970 (Slightly enlarged and retouched only to sharpen the outlines)

cellular exudates both with and without amebic infestation makes it impor tant to establish a differential diagnosis on the basis of microscopic study of bowel discharges

Appearance of Unstained Cells In unstained specimens cells are crystal clear and refractile Their nuclei appear as rings

Appearance of Stained Cells To prepare a specimen of bowel discharge with methylene blue for examination the technician should put a drop of Loffler s methylene blue on a slide and emulsify it with one or two drops of the bowel discharge When the methylene blue has penetrated the mucus the specimen should be covered with a coverslip and then examined under the low power objective It has a blue background on which the cells appear as small dots The character of the cells can be observed under the high dry or oil immersion objective they are definitely outlined and may be single or grouped together The methylene blue penetrates the nuclear structure readily so that in the wet preparation the nucleus may appear either as a ring of granules with a karyosome or else it may be a solid blue mass Brilliant cresyl blue may be used if available

Types of Cell Found in Cellular Exudates No cells will be found in the bowel discharges of patients when there is no pathologic change in the bowel wall but when pathologic change is present two well defined types of cell are found These types include

(1) *Polymorphonuclear leukocytes* These cells are frequently seen in the exudates of the bowel discharge In fresh unstained preparations their nuclei have the appearance of open rings there are usually two or three such nuclear rings in a single cell

When examined in the fresh unstained preparations these cells have fre quently been confused with encysted forms of *E histolytica* In order to dif ferentiate between the two forms it should be noted that while chromatoid bars characteristic of cysts of *E histolytica* can be visualized in fresh unstained preparations the nuclei of the ameba cannot Therefore if two or three promi nent nuclei can be observed it is probable that the cells are polymorphonuclear leukocytes

After the specimen has been stained with Loffler s methylene blue it should be re examined In this type of preparation the nuclei of the leukocytes will be observed to be either solid or else they may have open rings in which there is beading of the nuclear membrane Heavy granules of varying sizes and shapes are found both within the nucleus and in the cytoplasm It is also possible to determine whether the leukocytes are segmented or whether they are young forms

Whenever there is any suspicion that cysts of protozoa may be present in the specimen Lugol s solution should be used to bring out the nuclear struc ture The characteristic nuclear structure of the *E histolytica* cyst differs completely from that of the polymorphonuclear leukocytes and for that reason the examination with methylene blue and with Lugol s solution is of first importance in demonstrating the exact type of nuclear structure present

may be slightly displaced from the center and there may be some chromatin matter between it and the nuclear membrane

Encysted Forms (Cysts)

The cysts of *E histolytica* (Plates I and II) are produced by the secretion of a cyst wall around the precystic ameba This wall is about 0 5 micron in thickness and becomes smooth, transparent and colorless The cyst contains the cytoplasm nucleus and at times chromatoid bodies

Location Encysted forms of *E histolytica* are found in the lumen of the bowel and in the fecal mass

Size The average size of the encysted forms is 12 microns but the size varies from 5 to 20 microns according to the strain of the ameba

Shape Although not absolutely symmetrical the cysts are usually spherical but they may be oval or elongated

Ectoplasm The cyst wall is sharply defined and may have a greenish refractile appearance when freshly passed

Endoplasm The endoplasm is hyaline and smooth A glycogen vacuole may be present but usually the glycogen is used up during nuclear division No inclusions are present except at times chromatoid bodies

Chromatoid bodies The chromatoid bodies (Plates I and II) when present lie singly or in groups within the cytoplasm of the cysts they are important characteristics of the *E histolytica* cyst from the diagnostic point of view They are oval or rod shaped with blunt rounded ends and can be seen in saline unstained preparations but not in iodine preparations In stained preparations they are solid dark bodies They vary in number and size there may be as many as three present in the one cyst Their refractive index is *higher than that of the rest of the cyst and hence they can be readily* distinguished

Nucleus The number of nuclei in the *E histolytica* cyst (Plates I and II) varies from one to four cysts with eight nuclei are sometimes found In the mature cyst there are four nuclei which are often grouped in pairs at either side of the cyst Their structure is identical with that of the trophozoite forms They are sometimes bipolar in distribution and are difficult to see in the unstained living cyst At one pole of the nucleus in the two- and four nucleated cysts a characteristic condensation of chromatin causes the nuclear ring to appear to be *slightly thicker than elsewhere The karyosome is a delicate fine* dot of chromatin centrally placed within the clear zone inside the ring of finely beaded nuclear membrane

DIFFERENTIAL DIAGNOSIS OF AMEBAE

Cellular Exudates

The relationship of diarrhea to the different types of pathologic change in the bowel wall has not always been clear and consequently it has led to serious confusion in diagnosis Furthermore *the fact that it is possible to have*

acteristic of inflammatory reaction toxic necrosis and consequent autolysis are also absent In bacillary dysentery there is an abundance of cellular exudate (Fig 10) with a preponderance of polymorphonuclear over mononuclear cells there is evidence of toxic necrosis of cells the degenerative processes occurring early in all parts of the cell including the nucleus and frequently leaving only the circular periplast of the cytoplasm or ghost cell and there is evidence of phenomena characteristic of intense inflammatory reaction to microbe infection

Degeneration of Cells The cytoplasm if not too much degenerated contains numerous vacuoles in which there might be whole polymorphonuclear leukocytes red blood cells or fragments of them and bacteria all more or less digested The ingested leukocytes may be less degenerated than their hosts In some cells presumably the more degenerated the cytoplasm is not granular and vacuolated but swollen hyaline transparent apparently in a state of hydropic degeneration in which it will not absorb the iron alum hematoxylin stain This degenerative process begins very early in the cytoplasm which becomes successively granular vacuolated and hyaline There may be dots or granules greenish when fresh and black when stained with iron hematoxylin These dots are probably fragments thrust out from the pyknotic nuclei In fresh specimens they frequently exhibit distinct Brownian movements and can be mistaken readily for bacteria or other debris ingested by the cell

Like the cytoplasm the nuclei soon begin to show very definite karyorrhetic and karyolytic changes both in the fresh and stained specimens The nucleus swells first and then becomes granular next its center becomes transparent The chromatin matter is aggregated under the nuclear membrane leaving the center bare Following these changes the nucleus bursts and the resulting granules appear as a scattered line of irregular dots green in the fresh and black in the stained specimen Finally the dots disappear and the cell is marked by the periplast only which is usually circular

These endothelial macrophage cells possess feeble powers of ameboid movement a characteristic which can easily mislead the unwary These cells most closely resemble resting or dead amebae when the aggregation of chromatin granules are scattered around the periphery of the nucleus They have the appearance of large round cells vacuolated and containing ingested cells with a nucleus that shows the ringing which is a well marked characteristic of the amebic nucleus The two forms can be differentiated because in the degenerating ameba the nucleus is the last structure to disappear

Similar degenerative changes take place in the leukocytes and to a less extent in the mucosal cells Fatty degeneration is invariably present in exudate cells In the very early stages of the dysentery this change is extremely slight Intracorpuscular globules present in leukocytes and desquamated mucosal cells have the appearance of dustlike red granules when examined under the oil immersion lens and when Sudan III in alcoholic solution has been run in under the coverslip These globules enlarge until in advanced cases the greater part of the cell body is filled and even crammed with them This condition can

(.) *Epithelial cells* Methylene blue preparations are the simplest to use for the observation of epithelial cells These cells are of different sizes and shapes and their nuclei are either round or oval solid or ringed In some cases the nucleus resembles a solid mass when stained with methylene blue while in others it has the appearance of an open ring with fine beading and a central karyosome The cytoplasm is usually smooth and finely granular It may or may not have coarse masses of varying shapes

Amebic and Bacillary Dysentery

The history of the differential diagnosis of amebic and bacillary dysentery belongs to this century and is unfolded in the valuable researches of scientists working in the fields of parasitology bacteriology and pathology It was observed that there was a clear differentiation between the stools of amebic and bacillary dysentery both in appearance and under microscopic examination Amebic dysentery evacuations contain blood and mucus but they do not show the cellular exudate of the bacillary dysentery mucus Subsequent studies showed that the macroscopic and microscopic characters of the stool in the various stages of bacillary dysentery reflected the pathologic changes which occurred in the bowel wall

Bacillary Dysentery After the first intense congestion of the mucous membrane has taken place mucus is secreted which when examined shows large numbers of red blood corpuscles well preserved white corpuscles and a few epithelial cells The evacuations of the next stage consist mainly of bright red blood semi-opaque mucus and clear fluid which when observed under the microscope is seen to consist of a large number of red blood corpuscles leukocytes (often in small groups) and a few endothelial and epithelial cells In the next stage bright red blood no longer predominates because the pus cells begin to digest the entangling mucus and this process gives rise to an opaque fluid which when examined microscopically is found to consist almost entirely of pus cells After the fifth day in severe cases of bacillary dysentery coagulation necrosis and ulceration of the bowel mucosa begin and the bowel discharges become purulent Under the microscope it will be found that about 90 per cent are pus cells while the remainder consist of a few red blood cells lymphocytes endothelial and plasma cells If the bowel movements are kept liquid with saline purgation tags of grayish opaque mucus consisting of degenerated pus cells endothelial and epithelial cells can be seen with the naked eye If the stool is formed or soft it will have to be emulsified in saline before these cells can be observed

Cellular Exudate Differences in Amebic and Bacillary Dysentery Each type of cellular exudate in amebic (Fig 4) and bacillary dysentery (Fig 10) gives its own cytologic picture The character of the stool depends on the particular stage of the disease rather than on the nature of the food taken In amebic dysentery the cellular exudate is scanty especially the polymorphonuclear cells there is evidence of proteolytic digestion of the cells a process which begins at the periphery and affects the nucleus last of all All phenomena char

by trophozoite precystic and cyst stages of life and that multiplies most probably by simple fission

The *trophozoites* of *E coli* are characterized by sluggish movement and by the presence of numerous food vacuoles in which are found large numbers of bacteria also cysts of other protozoa and vegetable matter of all kinds *E coli* does not ingest red blood corpuscles or tissue cells a fact which serves to distinguish it definitely from the trophozoites of *E histolytica* It has a characteristic nucleus the chromatin matter of which is gathered into coarse beads and an eccentrically placed karyosome

The *precystic* form of *E coli* is relatively larger than that of *E histolytica* which it resembles it shows little inclination to movement of any kind and its cytoplasm is achromatic hyaline and free from food inclusions

The *encysted* form of *E coli* which appears when a cyst wall is secreted around a spherical precyst is distinguished by a clear cytoplasm and the presence of eight centrally placed nuclei with eccentric karyosomes and frequently with needle like chromatoid bodies

The *habitat* of the trophozoites of *E coli* is the lumen of the large intestine The tissues are not invaded the active forms living and multiplying in the contents of the upper colon while encystation takes place in the more solid contents of the lower part of the colon

Trophozoite Forms (Plate II)

Size Although the average diameter is between o and 30 microns which is larger than that of the *E histolytica* trophozoite the size of the trophozoite of *E coli* varies greatly ranging from 15 to 40 microns in diameter

Shape The shape of *E coli* varies considerably it is usually rounded but there is pseudopodia formation to enable movement of the trophozoite

Ectoplasm The ectoplasm of *E coli* is a heavily refractile layer enveloping the ameba but it is not as distinctly differentiated from the endoplasm nor as clearly defined as in the *E histolytica*

Endoplasm The endoplasm of *E coli* is achromatic granular to coarsely granular and contains a large number of food vacuoles in which all kinds of bacteria and vegetable debris are found but characteristically no red blood corpuscles or tissue cells The presence of these food vacuoles and the nature of their inclusions is a reliable means of identifying the ameba The trophozoites of *E coli* often contain vacuoles resembling clefts (some of them filled with a fluid substance) which differ entirely in appearance from the vacuoles found in degenerating forms of *E histolytica*

Nucleus The trophozoite of *E coli* can be recognized not only by its cytoplasm and characteristic inclusions but also by its nucleus which in contrast to that of *E histolytica* can be observed readily in the living ameba when prepared in normal saline Its nucleus has the appearance of a refractive ring of coarse granules larger and coarser in texture than the nucleus of the freshly passed *E histolytica* trophozoite The nuclear ring may be either round or oval in shape It measures from 4 to about 8 microns in diameter The nu

be seen in the green pea soup type of stool without obvious mucopus or blood which is characteristic of the advanced subacute stages of the disease In acute stages an extraordinarily small number of bacteria is observed to be present and the film resembles that from the pus of a streptococcal abscess rather than from a stool

Objects Often Found in Stools

Objects of various kinds that are found in stools often cause confusion in diagnosis and therefore must be carefully differentiated from amebae These include

(1) *Cells* Cells found in the stools come from the blood and also from the epithelial lining of the bowel Because the blood cells are found in a different medium from that of the blood plasma they are often difficult to recognize and to distinguish from amebae In cases of bacillary and amebic dysentery the cell picture helps in arriving at the correct diagnosis In true bacillary dysentery Charcot Leyden cells are not found although an amebic infection can be lost sight of in the heavy cellular exudate of bacillary dysentery The presence of Charcot Leyden cells is a reasonably reliable indication of amebic infestation

(2) *Tissue substances other than cells* Mucus comes from the tissues of the host in it groups of cells may be found also bacteria and the *E histolytica* of amebic dysentery when present The mucus itself is either clear or streaked and under a coverslip the streaks have the appearance of rings

(3) *Non protozoan organisms* The bacteria of the intestinal tract must be taken into account in differential diagnosis Organisms such as *Blastocystis hominis* are extremely common while in chronic colitis *Treponema eurygyrata* and *Treponema stenogyrata* are frequently observed

(4) *Organisms ingested by host* Free living organisms are frequently ingested by the host and these serve to confuse diagnosis Their presence can often be detected only after culture when their nature can be determined

(5) *Food objects of animal origin* Objects of animal origin are frequently found in the stools Fat globules may sometimes be mistaken for cysts Parasites that invade fish can pass intact through the human digestive tract and it is important not to mistake these organisms for amebae

(6) *Food objects of vegetable origin* Objects of vegetable origin are often the source of much confusion Chief among them are the oval fungus spores which can be readily confused with small strains of cysts Starch granules which stain blue sometimes give rise to error in diagnosis Pollen grains *spores of Tilletia tritici a parasite of wheat vegetable hairs* debris from rice peas beans and potatoes are often found and they have to be distinguished from protozoan forms which they sometimes simulate

ENDAMOEBA COLI

Endamoeba coli (Plates I and II) one of the larger protozoa to invade the human intestinal tract is a non pathogenic commensal that is characterized

by trophozoite precystic and cyst stages of life and that multiplies most probably by simple fission

The *trophozoites* of *E coli* are characterized by sluggish movement and by the presence of numerous food vacuoles in which are found large numbers of bacteria also cysts of other protozoa and vegetable matter of all kinds *E coli* does not ingest red blood corpuscles or tissue cells a fact which serves to distinguish it definitely from the trophozoites of *E histolytica* It has a characteristic nucleus the chromatin matter of which is gathered into coarse beads and an eccentrically placed karyosome

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cleus is eccentrically placed and its *chromatin matter gathered in the coarse* beaded ring is covered with a membrane which is also relatively coarse The eccentrically placed karyosome of the nucleus is larger than that of *E histolytica* it frequently measures as much as 1 micron in diameter Its halo is also larger and more clearly defined than that of *E histolytica* The differences between the nuclei of the amebae of *E coli* and *E histolytica* are apparent only *in the freshly passed forms* they disappear with the rapid degeneration of the *E histolytica*

Precystic Forms

Markedly sluggish precystic amebae which are very similar to those of *E histolytica* are formed when prior to encystation the trophozoites of *E coli* become reduced in size Their cytoplasm is hyaline and has no food inclusions

Location Precystic forms of *E coli* are found in the lumen of the large intestine

Size Larger than the corresponding forms of *E histolytica* the precysts of *E coli* measure from 15 to 20 microns in diameter

Shape The precystic forms of *E coli* are spherical

Ectoplasm The ectoplasm which touches the endoplasm appears as a sharp refractile and thickened line It has the same appearance when stained with hematoxylin and with Lugol s solution the iodine of which it absorbs

Endoplasm (cytoplasm) The endoplasm is granular and free from ingested material It reaches toward the ectoplasm

Nucleus The nucleus of the precystic forms of the *E coli* ameba resembles that of the trophozoite forms Thus the nucleus is more readily observed than that of *E histolytica* its chromatin matter is more abundant and its karyosome somewhat larger

Cyst Forms

The form of the mature *E coli* cyst commonly encountered is that which contains eight nuclei within a clear cytoplasm *In process of encystation the* precystic form becomes rounded and secretes a wall that is slightly thicker than that of *E histolytica* The nucleus increases in size and nuclear division continues until the characteristic eight nuclei are formed A glycogen vacuole *is formed at the binucleate stage but is absorbed before the cyst becomes* mature The mature cyst may contain numerous chromatoid bodies of irregular size and shape

Location The cysts of *E coli* live in the lumen of the large intestine

Size As a rule cysts of *E coli* measure from 15 to 20 microns in diameter although they may vary in size from 10 to 30 or more microns in diameter

Shape In shape cyst forms of *E coli* are spherical or slightly ovoid

Ectoplasm Because its ectoplasm is highly refractive and has a double outline the cyst of *E coli* is conspicuous in the fecal mass

Endoplasm The endoplasm of the *E coli* cysts is a distinguishing feature of the ameba at this stage in its life cycle It is granular and free from ingested substances Chromatoid bodies when present are filamentous or needle like

in form whereas in *E histolytica* these bodies are blunt with rounded ends In immature cysts glycogen masses may be found

Nucleus There are usually six or eight centrally placed nuclei distributed irregularly through the cytoplasm of the *E coli* cyst They have the same structure as the nuclei of the trophozoite forms a fact which is of greater importance for diagnosis than the number of nuclei present in the cyst With progressive nuclear division there is a decrease in the size of the nuclei in mature eight nucleated forms the size of each nucleus is about one fifth or one sixth that of the whole cyst The nuclear membrane is heavily beaded and the karyosome is also heavy Both nuclear membrane and karyosome can be readily observed in fresh unstained preparations It is important to observe that the karyosome is always eccentrically placed in contradistinction to the karyosome of the *E histolytica* which is invariably centrally placed

IODAMOEBA BUTSCHLII

Iodamoeba butschlii (Plates I and III) which so far has not been proved to be pathogenic to man is a relatively small intestinal ameba the life cycle of which includes trophozoite precystic and encysted forms

The *trophozoite* form of *I butschlii* when alive bears a marked resemblance both in form and habit to the small strains of *E coli* for which it is frequently mistaken It has the same pseudopoid formation and sluggish movement as the *E coli* but its nucleus is indistinct in the living ameba whereas that of *E coli* is readily seen It dies very soon after leaving its habitat

The *precystic* form of *I butschlii* unlike that of the corresponding forms of *E histolytica* and *E coli* does not decrease in size before encystation It becomes rounded inactive and gets rid of the contents of its food vacuoles so that its cytoplasm becomes clear otherwise it resembles the trophozoite form As it prepares to encyst its nucleus increases in size with the formation of additional chromatin granules in the region between the karyosome and the nuclear membrane

When alive the cyst of *I butschlii* is clear white in color and within its relatively thick wall are volutin granules and a glycogen mass Because of the reaction of this glycogen mass to iodine the term iodine cysts was formerly given to the encysted forms of *I butschlii*

The exact *habitat* of *I butschlii* is not known but it is most probably the large intestine

Trophozoite Forms (Plate III)

Size The average range in diameter of *I butschlii* is from 9 to 13 microns Large forms may measure as much as 20 microns in diameter and small forms as little as 5 microns

Shape The trophozoite form of *I butschlii* is irregular in shape Its pseudopodia are rounded and fairly broad

Ectoplasm The ectoplasm of *I butschlii* is hyaline but is not clearly differentiated from the endoplasm The pseudopodia are sluggishly extruded

Endoplasm The endoplasm is granular and has numerous large vacuoles

which may contain bacteria and very small vegetable cells *I butschlii* does not ingest red blood cells A large glycogen mass is usually present but it is not clearly distinguished until an iodine smear is made

Nucleus In the unstained living preparation the nucleus of *I butschlii* unlike that of *E coli* is extremely difficult to visualize but in stained preparations its nucleus has a characteristic structure which serves to distinguish it readily from other amebae that infest man Very small forms of *I butschlii* however may be almost if not quite impossible to distinguish from small uninucleated forms of *D fragilis*

When stained the nucleus of *I butschlii* is seen to be vesicular It measures between 2 and 3 5 microns in diameter approximately one fourth or one fifth the size of the trophozoite itself The karyosome which is usually centrally placed measures in diameter from one third to one half that of the nucleus *The karyosome stains deeply with iron hematoxylin but it is surrounded by* glycogen globules which do not retain the stain as well as the karyosome These globules frequently cause indentations in the karyosome and also affect its position within the nucleus The nuclear membrane which absorbs the stain readily is well developed and is separated from the karyosome by a zone which is usually clear in most amebae but which in *I butschlii* is marked by the presence of a layer of granules

Precystic Forms (Plate III)

Size Precystic forms are large some representing the largest size found in the *I butschlii* ameba

Shape Precysts of *I butschlii* are rounded up

Ectoplasm The ectoplasm of the precystic form is not clearly differentiated from the endoplasm it is sluggish to non motile

Endoplasm Clear of all food inclusions the endoplasm becomes transparent

Nucleus The nucleus of *I butschlii* precysts increases in size from about or 2 5 microns in diameter—which is characteristic of the trophozoite form—to 3 microns or more through the formation of additional layers of granules between karyosome and the nuclear membrane Otherwise the structure of the nucleus and karyosome resembles that of the trophozoite form

Encysted Forms (Cysts) (Plates I and III)

Size Although oval and spherical cysts of *I butschlii* vary in size from 7 to 15 microns in diameter their average size is from 8 to 10 microns in diameter

Shape The living cysts of *I butschlii* are usually spherical or ovoid but they often exhibit marked irregularities in form

Ectoplasm The ectoplasm forms a definitely refractile wall around the cyst of *I butschlii*

Endoplasm The endoplasm of the encysted form of *I butschlii* is granular It contains a large oval area which is filled with glycogen and which appears as a clearly defined dark brown mass when stained with iodine When stained with iron hematoxylin the glycogen mass has the appearance of any

empty vacuole The endoplasm also includes a number of bright refractile granules which are chemically different from similar bodies in the *Endamoeba* The granules of *I butschlii* cysts are either of volutin or else of a substance akin to volutin

Nucleus As a rule there is only one nucleus in cysts of *I butschlii* although encysted forms with two nuclei are sometimes found The nucleus lies between the cyst wall and the glycogen mass within the thickest part of the cytoplasm The nuclear membrane is well developed The karyosome which has the appearance of a large solid mass is not centrally located as it is in the trophozoite form but lies against the nuclear membrane The globules that surround the karyosome in the trophozoite fill the remainder of the nuclear membrane in the encysted form

ENDOLIMAX NANA

Endolimax nana (Plates I and III) which is one of the commonest of the non pathogenic intestinal amebae is a small protozoan about one half the size of *E coli* the life cycle of which consists of trophozoite precystic and encysted stages

The *trophozoite* of *E nana* is active when freshly passed but it rapidly becomes sluggish and then ceases to move altogether The characteristic nucleus which is different in structure from that of the *Endamoeba* cannot be seen readily in the living organism *E nana* has no contractile vacuoles but it has numerous food vacuoles that are filled with micro organisms

The *precystic* forms do not differ perceptibly from the trophozoite forms except for the fact that they have no food inclusions and consequently their cytoplasm is clear

The *cysts* of *E nana* are formed when the precysts become oval or rounded and are encased within a smooth thin cyst wall They have a characteristic structure and contain four nuclei when mature They are sturdy and will not deteriorate for some weeks if kept moist in the human feces In saline preparations these cysts have the appearance of clear uniform organisms The structure of the nuclei is brought out with fixed staining preparations

E nana is an inhabitant of the lumen of the large intestine It does not invade the tissues of the intestine

Trophozoite Forms (Plate III)

Size Trophozoites of *E nana* range in size from 6 to 15 microns in diameter the average being from 8 to 10 microns in diameter The fact that they are about half the size of *E histolytica* and *E coli* is important for diagnostic purposes

Shape *E nana* trophozoite forms show considerable variation in shape Finger like pseudopodia become short and blunt as the organism loses its active motility and becomes sluggish

Ectoplasm The ectoplasm is a thin hyaline wall that surrounds the parasite

Endoplasm (*cytoplasm*) The endoplasm of the *E nana* trophozoite is not

clearly differentiated from the ectoplasm It is granular and vacuolated The ameba ingests bacteria as well as other material from the bowel by means of food vacuoles

Nucleus The trophozoites of *E nana* usually have a single nucleus which is very difficult to see in unstained preparations In stained preparations the nucleus is seen to be from 2 to 3 microns in diameter It is a vesicular structure and is separated from the cytoplasm by a well defined nuclear membrane which is usually free from chromatin matter The chromatin in the nuclear structure of *E nana* is collected in the granules of the karyosome and hence is not present in the nuclear membrane This is characteristic of *E nana* and makes it possible to distinguish it from organisms such as small strains of *E histolytica* A clear zone is present between the nuclear membrane and the karyosome The karyosome itself is the most important distinguishing feature of the trophozoite of *E nana* It displays marked irregularity both in form and structure It is usually eccentrically placed and has the appearance of a large irregular mass connected by filaments with smaller masses These characteristics of the nucleus of *E nana* can be seen only in freshly passed specimens The nuclear structure changes rapidly with the deterioration of the ameba The segments of the karyosome come together into one mass and touch the nuclear membrane at one pole This gives the nucleus a signet ring appearance

Precystic Forms

Size Precystic forms of *E nana* are about the same size as the trophozoites

Shape In shape precysts of *E nana* are rounded or oval

Ectoplasm Thin hyaline wall not readily visualized

Endoplasm There are no food vacuoles in the precystic forms of *E nana* and bacteria are absent Consequently the cytoplasm is clear Otherwise the endoplasm is the same in structure as that of the trophozoite form

Nucleus The nucleus of the precyst forms of *E nana* is visible as a refractive mass of chromatin

Encysted Forms (Cysts) (Plates I and III)

Size Encysted forms of *E nana* are about the same size as the trophozoite and precystic forms measuring from 8 to 10 microns in length and from 5 to 8 microns in width

Shape The cysts of *E nana* are slightly asymmetrical they are usually oval in shape although they are sometimes spherical

Ectoplasm The ectoplasm is not separated from the endoplasm It makes a sharp refractile line outlining the cyst

Endoplasm The endoplasm is finely granular and is free from ingested material

Nucleus The nucleus is not readily seen in unstained preparations but it may appear as an irregular mass of chromatin matter within a clear area of cytoplasm When newly formed the cyst contains a single nucleus and several minute refractile granules composed either of volutin or a similar substance

Chromatoid bodies are not present The number of nuclei in encysted forms of *E nana* varies from one to four In mature cysts there are usually four nuclei The nucleus frequently measures as much as 3 microns in uninucleated cysts but in the mature quadrinucleated cyst the nuclei measure about 1 micron in diameter In the process of division the nuclei become reduced in size but otherwise retain the characteristics of the nuclear structure found in the trophozoite form The nuclei are found in almost any position with the cyst but usually they are grouped together at one end

DIENTAMOEBA FRAGILIS

Dientamoeba fragilis (Plate III) is a small intestinal ameba that is characterized by active motility when freshly passed and by the rapidity with which it degenerates when outside its host and that so far is known to occur in the trophozoite life stage only

When in motion *D fragilis* has a snail like appearance its pseudopodia are in front like the horns of the snail while in the rear its endoplasm assumes the form of a rounded mass It has numerous vacuoles and ingests bacteria and other micro-organisms but it does not ingest red blood corpuscles Its two nuclei identical in size and structure which are not readily seen in unstained preparations constitute its most characteristic feature When the organism begins to degenerate it becomes vacuolated the vacuoles coalesce and the vacuole so formed is embedded within a thin layer of protoplasm At this stage the *D fragilis* ameba may be readily confused with *B hominis*

Location The habitat of *D fragilis* is thought to be the colon The ameba is found in the fecal mass

Size *D fragilis* is a very small ameba which ranges in size from 5 to 10 microns in diameter the average being from 8 to 9 microns

Shape The shape of the *D fragilis* ameba is variable Leaf shaped or lobulated pseudopodia are extruded The organism tends to become rounded as degeneration sets in

Ectoplasm The ectoplasm of *D fragilis* is clearly defined from the endoplasm Hyaline pseudopodia composed almost entirely of ectoplasm are pushed out spread laterally and flattened and consequently assume a leaf like or lobed appearance There is little actual movement of the ameba since the pseudopodia are forced out in all directions

Endoplasm The endoplasm of *D fragilis* is finely granular and vacuolated Bacteria and minute vegetable particles are found in the food vacuoles There is no contractile vacuole in this ameba

Nucleus About four out of every five trophozoites of *D fragilis* are binucleated the other forms have one nucleus only The nuclei are difficult to detect in unstained preparations When stained with iron hematoxylin they are observed to vary in size from 0 8 to 3 microns They are spherical in shape and vesicular in structure Nuclear chromatin matter is collected in the centrally placed karyosome Upon examination the karyosome is seen to be composed of a group of small irregular granules of chromatin which are appar

ently embedded in a plastin matrix *No chromatin matter is present on the inner surface of the very delicate nuclear membrane* A clear zone separates the karyosome from the nuclear membrane which envelops the nucleus In well stained specimens it is possible to see very fine linin threads

BLASTOCYSTIS HOMINIS

B hominis a common intestinal parasite is a sluggish vegetable cell

B hominis is a medium sized organism that is enveloped in a covering membrane It has a large central area filled with a transparent or finely granular substance The peripheral layer of cytoplasm in which the two or more nuclei and refractive granules are embedded is clearly differentiated from the contiguous central area

Location The habitat of *B hominis* is the intestine

Size The size of *B hominis* is usually from 10 to 15 microns in diameter but may vary from 5 to 40 microns in diameter

Shape B hominis parasites are spherical or oval in outline the dividing form is shaped like an hourglass

Cytoplasm The outer layer of cytoplasm which is semilunar in form contains large refractile globules of volutin and the nuclei which are frequently refractile also The inner layer is thin and lies around the inside of the cell membrane When the peripheral layer with its granules lies uppermost in the organism a striking resemblance can be observed between the granules *of the B hominis and the nuclei of true amebae This marked resemblance* leads to confusion in diagnosis especially with cysts of *E histolytica*

Nucleus One or more small nuclei are located at each pole of the organism Each one has a large central vacuole usually non refractile but sometimes refractile and with a yellowish or brownish color

BALANTIDIUM COLI

B coli (Plates IX and X) is a tissue parasite of the ciliate class that is found in trophozoite and cyst forms and that multiplies by binary fission

The *B coli* trophozoite is the largest protozoan to invade the human intestine Like other ciliates this organism is covered with longitudinal rows of cilia which become stiffer and longer in the region of the peristome and cytostome and are in constant motion This parasite produces ulcerative lesions of the bowel The cytoplasm of *B coli* is characterized by the presence of a macronucleus and a micronucleus and also of food vacuoles

The cyst of B coli is large and has a fairly thick tough wall composed of two layers the outer of which is the thicker of the two Before encystation the parasite absorbs or eliminates the contents of its food vacuoles and following encystation it revolves rapidly for some time within the cyst wall before coming to a halt *Soon the cilia degenerate and the outline of the organism is lost* The cytoplasm of the cyst appears to be granular and to contain the macronucleus

B coli trophozoites are located in the mucous membrane of the large bowel They make their way through the epithelium of the large and sometimes of the small intestine to the submucous membrane where they encyst and multiply

Trophozoites

Size There is considerable variation in the size of *B coli* The average length is from 50 to 80 microns and the average breadth from 40 to 60 microns Some specimens are as long as 100 microns It is possible although it has not yet been proved that there are large and small strains of this ciliate

Shape *B coli* trophozoites are oval and slightly asymmetrical in shape The anterior end is pointed and is characterized by the presence of a cytostome an organelle which leads into a gullet or esophagus The parasite usually retains its shape which however may be affected by the pressure of objects surrounding it owing to its lack of rigidity

Ectoplasm The ectoplasm consists of a clear delicate pellicle covered with cilia which run longitudinally in rows from basal granules

Endoplasm Food vacuoles and two nuclei can be observed within the granular endoplasm of the *B coli* trophozoite Food is ingested through the cytostome and passes through the gullet to the endoplasm where it is surrounded by a liquid substance In this manner food vacuoles are formed During digestion these vacuoles move around in the endoplasm The *B coli* trophozoite ingests all kinds of material including fecal debris red blood corpuscles leukocytes tissue fragments and starch grains Two contractile vacuoles which pulsate slowly and regularly are also present in the endoplasm

Nucleus Within the endoplasm of the *B coli* trophozoites are the kidney shaped macronucleus and the spherical micronucleus The macronucleus lies in a transverse position near the center of the cytoplasm Chromatin granules are densely packed within it and are covered by a clearly defined nuclear membrane The micronucleus is very small It lies in contact with or very near to the concavity of the macronucleus

Cyst Forms

The cyst form contains a single *B coli* which revolves for some time within the cyst wall It is slightly yellowish in color When the parasite has ceased revolving its form changes so that the cyst appears to be filled with granular cytoplasm a macronucleus and a contractile vacuole Later the vacuole disappears

Location The cysts of *B coli* are formed in the intestine They pass out of the system with the feces

Size *B coli* cysts are the largest protozoal cysts found in the human intestine and measure from 50 to 60 microns in diameter

Shape The cysts are round or slightly oval in shape

Cytoplasm and Nucleus The most distinctive feature of the granular cytoplasm is the macronucleus which can be seen clearly in properly stained

ently embedded in a plastin matrix No chromatin matter is present on the inner surface of the very delicate nuclear membrane A clear zone separates the karyosome from the nuclear membrane which envelops the nucleus In well stained specimens it is possible to see very fine linin threads

BLASTOCYSTIS HOMINIS

B hominis a common intestinal parasite is a sluggish vegetable cell

B hominis is a medium sized organism that is enveloped in a covering membrane It has a large central area filled with a transparent or finely granular substance The peripheral layer of cytoplasm in which the two or more nuclei and refractive granules are embedded is clearly differentiated from the contiguous central area

Location The habitat of *B hominis is the intestine*

Si e The size of *B hominis* is usually from 10 to 15 microns in diameter but may vary from 5 to 40 microns in diameter

Shape B hominis parasites are spherical or oval in outline the dividing form is shaped like an hourglass

Cytoplasm The outer layer of cytoplasm which is semilunar in form contains large refractile globules of volutin and the nuclei which are frequently refractile also The inner layer *is thin and lies around the inside* of the cell membrane When the peripheral layer with its granules lies uppermost in the organism a striking resemblance can be observed between the granules of the *B hominis* and the nuclei of true amebae This marked resemblance leads to confusion in diagnosis especially with cysts of *F histolytica*

Nucleus One or more small nuclei are located at each pole of the organism Each one has a large central vacuole usually non refractile but sometimes refractile and with a yellowish or brownish color

BALANTIDIUM COLI

B coli (Plates IX and X) is a tissue parasite of the ciliate class that is found in trophozoite and cyst forms and that multiplies by binary *fission*

The *B coli* trophozoite is the largest protozoan to invade the human intestine Like other ciliates this organism is covered with longitudinal rows of cilia which become stiffer and longer in the region of the peristome and cytostome and are in constant motion This parasite produces ulcerative lesions of the bowel The cytoplasm of *B coli* is characterized by the presence of a macronucleus and a micronucleus and also of food vacuoles

The *cyst of B coli* is large and has a fairly thick tough wall composed of two layers the outer of which is the thicker of the two Before encystation the parasite absorbs or eliminates the contents of its food vacuoles and following encystation it revolves rapidly for some time within the cyst wall before coming to a halt Soon the cilia degenerate and *the outline of the organism* is lost The cytoplasm of the cyst appears to be granular and to contain the macronucleus

plasts while the last pair thicker than the others arises from the central blepharoplasts and lie parallel to each other on the surface of the parasite s body The arrangement of these pairs of flagella can be observed in stained preparations

Cytoplasm The achromatic cytoplasm is finely granular There are no food vacuoles in the endoplasm which is not clearly differentiated from the ectoplasm

(1) *Axonemes* The axonemes of the four pairs of flagella arise from blepharoplasts The varied descriptions of the arrangement of these appendages of the flagellate given by different authorities indicate the difficulty en countered in tracing their exact locations Two axonemes which arise from the lateral blepharoplasts take a forward course then cross one another and then extend to the sucking disc the edge of which they follow until they enter the flagella Two other axonemes which are sometimes called the axostyles of *G lamblia* arise from the median blepharoplasts and go backward on the surface or just beneath the surface of the parasite s body to the posterior flagella A third pair of axonemes arises from the central blepharoplasts and enters the flagella immediately while a fourth pair of axonemes can be traced forward to the notch of the sucking disc where they terminate in granules at the end of the notch

(2) *Axostyles* Although not true axostyles such as those of the *Tri chomonas* the two axonemes which originate in blepharoplasts lying in front of the anterior poles of the nuclei and which pass to the posterior end of the parasite are usually regarded as such A rod which stains a dark color is frequently present and is observed lying across the axostyles

(3) *Blepharoplasts* The blepharoplasts from which the axonemes arise are located on the ventral surface of the parasite Two blepharoplasts lie in front of the anterior poles of the nuclei and four more arranged in pairs lie be tween the nuclei one pair located centrally and the other slightly posteriorly There are probably two additional blepharoplasts from which the axonemes of the fourth pair of flagella arise

Cytostome No cytostome is present in G *lamblia* although the sucking disc is sometimes wrongly referred to as such

Nucleus In the trophozoite of *G lamblia* two nuclei are present one lying on either side of the ventral median line of the parasite near the sucking disc. The nuclei are oval in shape and vesicular in structure Within the nuclear membrane is the karyosome which is frequently elongate in form In some specimens of apparently older trophozoites the nuclear structure also con tains separate chromatin masses that are linked together by fine fibers On the anterior surface of the nuclear membrane lies the granule in which the anterior axonemes terminate

Cyst Forms

Size The average size of cysts of *G lamblia* is 10 by 7 microns They may range however from 8 to 12 microns in length by 7 to 10 microns in breadth

specimens Irregular refractile bodies and a posterior vacuole that pulsates rhythmically can also be seen in the earlier stages of the cyst

FLAGELLATES

GIARDIA LAMBLIA

G lamblia (Plates I and V) is a parasitic flagellate that infects vertebrates It is characterized by morphologically distinctive trophozoite and cyst stages of life and like other flagellates it multiplies by longitudinal binary fission

Typical *trophozoites* of *G lamblia* have pear shaped symmetrical bodies which are broad and rounded at the anterior end and taper posteriorly The dorsal surface is convex and its ventral surface is flattened It has a well defined *ventral sucking apparatus from which four of the eight flagella arise* In addition to the eight flagella the *G lamblia* trophozoite has eight corresponding axonemes It has typically two nuclei which can be observed within the achromatic cytoplasm

Cyst forms of *G lamblia* are oval in shape The cyst wall covers the anterior end of the vegetative form first then extends backward and finally encloses the tail In newly formed cysts the movement of the tail and flagella can be observed

The trophozoites of *G lamblia* are found in the upper part of the small intestine and in the duodenum where they adhere to the mucous membrane by means of suckers which are attached to their ventral surface They have also been found in the tubules of the intestinal secretory glands and even in the gall bladder Cysts of *G lamblia* are found in the lower part of the gut *especially in the large intestine They are found in the formed stool* whereas the trophozoites are more usually found in fluid or semifluid stools

Trophozoites

Size There are both large and small strains of *G lamblia* and consequently the size of this flagellate varies considerably In length excluding the tail flagella it measures from 10 to 18 microns and in breadth from 5 to 10 microns

Shape When the *G lamblia* trophozoite is lying flat it has been aptly described as resembling a longitudinally split pear The dorsal surface of this genus is convex while the ventral surface is flattened *The posterior tail* is flexible but the rest of the body is rigid

Motility In fluid media the trophozoites of *G lamblia* move forward with a slightly rocking movement Freshly passed trophozoites are active but later *their* movements become sluggish

Undulating Membrane No undulating membrane is present in the trophozoites of *G lamblia*

Flagella Trophozoites of *G lamblia* have four pairs of flagella which originate in blepharoplasts One pair of lateral flagella is crossed and another pair is uncrossed Both pairs arise from lateral blepharoplasts *A third pair of* flagella is situated posteriorly and arises from the anterior median blepharo-

Undulating membrane Some authorities regard the flagellum within the cytostome as the border of an undulating membrane

Flagella C *mesnili* trophozoites have three anterior flagella which are about the same length as the organism itself and which originate in a group of blepharoplasts From a posteriorly situated blepharoplast arises a flagellum which is thicker than the anterior flagella It moves rhythmically within the cytostomal groove and assists in capturing food particles for the organism

Cytoplasm The cytoplasm is usually colorless or tinged with a faint green It is finely granular The endoplasm is moderately dense and is not distinguished from the ectoplasm A thin well defined pellicle which may contain vacuoles passes through the endoplasm The cytostome which extends backward for almost half the length of the flagellate marks the central surface of the cytoplasm

(1) *Axonemes* Three of the six blepharoplasts are anteriorly placed and from each of these an axoneme arises These axonemes pass forward to the anterior surface of the flagellate where they enter the three anterior flagella

(2) *Axostyles* No axostyles are present in the trophozoite of *C mesnili*

(3) *Blepharoplasts* There are six blepharoplasts three anterior and three posterior which are so closely packed together that they have the appearance of a single deeply staining body They are slightly in front of the anteriorly placed nucleus and also of the beginning of the cytostomal cleft From the three anterior blepharoplasts arise three axonemes and from the midposterior blepharoplast arises the flagellum which is placed in the cytostomal cleft The left posterior blepharoplast gives rise to a fiber which stains deeply and which passes along the left edge of the cytostomal cleft around the posterior end and up the right edge for a short distance The fiber from the right posterior blepharoplast lines the right edge of the cleft until it approaches the meeting point with the fiber coming from the other direction

Cytostome The cytostomal cleft is about half the length of the body of the C *mesnili* trophozoite and the cytostome or mouth is located at the posterior end of the cleft at the point at which the fiber which edges the cytostomal cleft curves from left to right The buccal apparatus of the flagellate consists of the slightly spiral cleft which runs lengthwise from the anterior end The edges of this cleft form two well marked irregular lips which are supported by fibers from the posterior blepharoplasts

Nucleus The nucleus is usually either round or oval and is situated anteriorly It has a thin nuclear membrane and contains a linin network There may be chromatic granules between the eccentrically placed karyosome and the nuclear membrane and there may also be some chromatin at one pole

Cyst Forms

When cysts of C *mesnili* are freshly passed and unstained their internal structure is practically undistinguishable When stained the cyst form is observed to have the same structural features as the trophozoite form The cytostomal cleft containing a flagellum runs lengthwise the nucleus is

Shape Cysts of *G lamblia* are oval in shape

Cytoplasm The cyst wall of *G lamblia* is smooth and well defined resembling a double line surrounding the cyst The ectoplasm is refractile and the endoplasm is finely granular In young cysts the mass of cytoplasm may contain in addition to four nuclei fibrils which constitute the margin of the sucking disc and which are coiled at the end of the cytoplasm opposite the nuclei

Nucleus The two nuclei of the *G lamblia* trophozoite move to the anterior end of the cytoplasm where they divide Four round nuclei arranged in pairs are thus formed They have a well defined nuclear membrane with a small but definite karyosome which is either centrally or eccentrically located

CHILOMASTIX MESNILI

C mesnili (Plates I and V) is an apparently non pathogenic intestinal flagellate *which is found in morphologically distinctive trophozoite and cyst* stages of life and which multiplies by binary fission in the long axis after nuclear division has taken place

The *trophozoites* of *C mesnili* are asymmetrical pear shaped actively motile organisms Their anterior end is rounded while the posterior extremity tapers to a sharp point A spiral groove begins near the cytostomal opening and passes round the body It may terminate at the posterior end of the cytostome but may continue further and make a second spiral around the body of the parasite This spiral groove tends to give the flagellate a twisted appearance in the posterior region

Cyst forms of *C mesnili* are more nearly ovoid in shape than the trophozoites In stained preparations the details of the organism can be clearly distinguished The cytostomal cleft is readily seen also the blepharoplasts and near them the *nucleus which is situated in the narrow end of the cyst*

Trophozoites of *C mesnili* are found in the mucosa and lumen of the glands of the large intestine They may be present also in the small intestine They are not known to invade the intestinal tissues Cyst forms of *C mesnili*, which are often found in the stool are present in the large intestine and possibly also in the small intestine

Tropho oites

Size Trophozoites of *C mesnili* vary considerably in size They measure from 6 to 20 microns in length and from 3 to 10 microns in breadth Small forms may be *not more than 3 to 4 microns in diameter*

Shape *C mesnili* trophozoites are pear shaped but are somewhat asymmetrical They have a rounded blunt anterior end and a tapering posterior end The shape of the posterior end varies it may be blunt or it may taper and have a tail like projection

Motility When freshly passed the *C mesnili* trophozoite is actively motile It has a typical jerky progressive movement Its cytostomal groove is kept moving toward any food particles that may be present in the *fluid that surrounds it*

blepharoplasts located one in front of the other and situated near the nucleus Three flagella arise from the anterior blepharoplast The posterior blepharoplast is near the flattened side of the organism and from it arises the fourth flagellum which traverses the flattened lateral margin and projects itself as a free flagellum for a short distance

Cytoplasm When the trophozoite is stained with hematoxylin its cytoplasm is alveolar in appearance A well defined nucleus can be observed within the cytoplasm

(1) *Axonemes* The axonemes of the flagella originate in two blepharoplasts which are situated at the apex of the nuclear membrane

(2) *Blepharoplasts* These are two in number From the anterior blepharoplast arise three flagella and from the posterior blepharoplast another flagellum arises

Nucleus The nucleus located near the anterior end of the organism is single It is vesicular in structure and spherical in shape Generally it measures from 1 5 to microns in diameter Its karyosome is large and centrally placed The nuclear membrane follows the spherical shape of the nucleus

Cyst Forms

Size Cyst forms of *T intestinalis* are small measuring from 6 to 8 microns in length and from 4 to 6 microns in breadth

Shape Cysts of *T intestinalis* are usually oval in outline resembling fungus spores in appearance

Nucleus Cysts which have a well-defined wall are observed when stained to have one nucleus or else two or four nuclei The nuclei are arranged at opposite poles of the cyst and they are seen to have a central karyosome and a clearly defined nuclear membrane

TRICHOMONAS HOMINIS

T hominis (Plate V) is one of the commonest intestinal flagellates in man and is found in the trophozoite form only These forms multiply by longitudinal division after binary fission of the blepharoplast and the nucleus

T hominis can be recognized readily because it is the only intestinal flagellate with an undulating membrane It is a relatively small organism and it varies considerably in shape because of its active motility When motility ceases the parasite becomes rounded up

Location The habitat of the *T hominis* trophozoite is both the large and small intestine

Size The average length of the *T hominis* trophozoite is from 10 to 1° microns although individuals may range from 7 to 15 microns in length This flagellate readily shrinks in size upon fixation

Shape Because of their plastic nature the trophozoites of *T hominis* vary considerably in shape They are usually rounded or oval in shape frequently their posterior end tapers and terminates in a protruding axostyle

Motility The *T hominis* flagellate moves forward jerkily it is actively

located near the narrow end of the cyst and nearby are the blepharoplasts

Location Cysts of *C mesnili* which are frequently found in the stools are located in the large and possibly also in the small intestine

Size The cysts of *C mesnili* vary in size from 7 to 10 microns in length and from 4 5 to 7 microns in breadth

Shape In shape the cysts of *C mesnili* are ovoid and are usually narrower at one end than at the other They have a nipple like projection at the narrower end

Cytoplasm In stained specimens the cytoplasm is observed to be finely granular It contains two fibrils and a flagellum which constitute the remains of the cytostome and which appear as black lines within the cyst Like the blepharoplasts these structures may assume the form of black granules within the cytoplasm

Nucleus There is a single nucleus located either in the center of the cytoplasm or toward the narrow end of the cyst The nuclear membrane is well defined and the karyosome is centrally placed Chromatin masses with traces of linin network are usually distributed within the nuclear membrane and in some cases chromatin masses are also found to one side of the nucleus

TRICERCOMONAS INTESTINALIS

T intestinalis (Plate V) is an extremely active intestinal flagellate that is found in trophozoite and cyst stages of life and that reproduces by longitudinal division

The *trophozoite* of *T intestinalis* is a relatively small colorless pear shaped organism It has three anterior flagella and one posterior flagellum Its single nucleus is spherical in shape so that the nuclear membrane is drawn out into a cone

Cyst forms of *T intestinalis* are sometimes found They are small and have a distinct cyst wall When stained the cysts may be observed to have from one to four nuclei

The exact location of *T intestinalis* has not been determined The parasites are found in diarrheal stools

Trophozoites

Size In length the trophozoite of *T intestinalis* usually measures from 7 to 8 microns *although it may vary from 4 to 10 microns In breadth* it measures from 3 to 6 microns

Shape The *T intestinalis* trophozoite is pear shaped in appearance It has a blunt rounded anterior end Its posterior end terminates in an extremely *fine point and the flagellum* may be continued for a short distance further than this point One side of the organism is convex while the other is flattened and may have a longitudinal groove

Motility When freshly passed this parasite is extremely active Its movements are jerky

Flagella Trophozoites of *T intestinalis* have four flagella There are two

forms resembling in all details the intestinal *T hominis* The parasite has an undulating membrane and usually four flagella are found to be present

Location *T vaginalis* is found in acid vaginal secretion but not in alkaline secretion

Size Large and small strains of *T vaginalis* exist They measure from 18 by 6 microns in small strains to 26 by 16 microns in the larger ones

Shape *T vaginalis* is identical in shape with *T hominis* Its forms vary from long and narrow to almost spherical

Motility *T vaginalis* is actively motile a characteristic by which it can be diagnosed

Undulating membrane In the large spherical forms the undulating membrane extends only about one half the length of the flagellate In small forms however it is as long as the body itself The membrane is about the same length in both forms

Flagella Flagella vary in number from three to five but usually four are found

Cytoplasm (1) An axoneme which is attached to the undulating membrane terminates at the posterior end of the cytoplasm

(2) An axostyle extends from the region of the nucleus to the posterior end of the parasite and then extends beyond it for a short distance

Cytostome A definite cytostome has been observed in some specimens of *T vaginalis*

ISOSPORA HOMINIS

Location and life cycle *Isospora hominis* (Plate VII) is parasitic for the small intestine of man Although the life cycle of the parasite has not been actually worked out it is believed that the oocysts are ingested by man after which they liberate sporozoites which penetrate the cells of the intestinal villi Schizogony and eventually sporogony take place and finally oocysts are developed and these are passed with the feces When the oocysts are swallowed the cycle is repeated

Size The oocysts found in human stools vary in length from 20 to 32 or 33 microns and are from 10 to 19 microns in breadth

Shape They are generally oval and elongated some slender and long while others are more spherical An indentation often occurs at both ends giving the appearance of a bulge in the center This indentation may occur at one end only

Contents of the cysts Immediately after being passed the cysts are usually non segmented and the contents of the oocyst are usually contracted into a central spherical mass Occasionally oocysts can be seen which have undergone development The central mass divides into two sporoblasts each one of which gives rise to a sporocyst In the mature sporocyst there are four sporozoites and also a large mass of residual material

motile Its flagella lash from side to side with great vigor while its undulating membrane causes its body to revolve continuously on its longitudinal axis

Undulating membrane The trophozoites of *T hominis* have a well-developed undulating membrane which originates in a blepharoplast at the anterior end of the body and runs in a slight spiral along the dorsal surface to the posterior end When movement is sluggish the tips of the undulating membrane only can be seen Its base is secured by a fiber which arises from the blepharoplast and a flagellum extends along its free edge

Flagella There are usually *four flagella although three or five are often* found The flagella may be as long as or longer than the body of the *T hominis* trophozoite They originate in the blepharoplasts and their proximal portions frequently appear to be twisted to form a stem When in action the flagella move from side to side of the parasite in sweeping movements

Cytoplasm The ectoplasm of *T hominis* is not distinguishable from the endoplasm The endoplasm contains numerous vacuoles The single nucleus is visible through the colorless cytoplasm The parasite ingests bacteria and sometimes also red blood corpuscles through a small mouth or cytostome which is located anterolaterally

(1) *Axonemes* The name axoneme was given by Wenyon (19 6) to the root and attached portions of all flagella The axoneme of *T hominis* is located on the free edge of the undulating membrane It is attached to the body of the parasite by means of a firm basal fiber Sometimes it extends beyond the undulating membrane in which case it forms an additional flagellum The axoneme moves in ripples

(2) *Axostyles* An axostyle which has the appearance of a broad bar develops from a blepharoplast It passes around the nucleus goes centrally down the long axis of the body and then projects itself as a flexible spike at the posterior end

(3) *Blepharoplasts* In stained specimens a group of three or more blepharoplasts can be observed anterior to the nucleus From these arise the undulating membrane the basal fiber the axostyle and also the axonemes of the flagella

Cytostome The small cytostome or mouth is situated anterolaterally In stained preparations the cytostome remains unstained

Nucleus The nucleus which *is usually invisible in* unstained preparations and while the parasite is alive is small and is either round or slightly oval in shape It is located near the anterior end of the cytoplasm It is vesicular and contains a linin network on which many chromatin granules may be found The nucleus has a central karyosome and a thin nuclear membrane

TRICHOMONAS VAGINALIS

T vaginalis is an active flagellate found by means of cultures to be identical with the *Trichomonas* which invade the mouth and intestine

The *T vaginalis flagellate is found in* large and small strains the smaller

PATHOLOGY

It is a moot question as to whether or not pathologic lesions are produced by *G lamblia* Some observers have asserted that the parasites are found in large numbers in the active diarrheas in which the stools are liquid Symptoms of gastro enteritis are apparently present in some of these patients and the suspicion of pathogenicity is strengthened by the fact that mucus containing large numbers of this parasite is frequently passed in the stools This suspicion is further strengthened by the fact that specific therapy is followed by relief of the symptoms *G lamblia* are frequently found in the bile obtained during gall bladder drainages

SYMPTOMATOLOGY

There is no typical clinical picture of *G lamblia* infections but in most cases the patients complain of diarrhea in varying degree stools occurring from two to six times daily Mucus is quite frequently present Flatulence abdominal distention anorexia alternating diarrhea and constipation abdominal pain and tenderness are symptoms which have been described

DIAGNOSIS

The diagnosis is made by the discovery and demonstration of *G lamblia* in the feces The trophozoites occur only in fluid stools while the cysts are found in the formed stools The diagnostic methods that are used for the examination of stools for amebae should be followed for the discovery of *G lamblia*

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of *G lamblia* includes all other conditions which may be associated with the symptoms of diarrhea That other conditions may also be associated with *G lamblia* infections has to be borne in mind in the evaluation of any case Thus in one instance in a single family the mother had an infection with *E histolytica* with no symptoms whatever and her child complained of diarrhea with blood and mucus in the stools Search of fifteen stool specimens of the child failed to reveal any *E histolytica* forms but only a heavy *G lamblia* infection Proctoscopic examination of the child revealed an ulcerating polyp in the sigmoid colon A cure was effected by treating the child with atabrine followed by removal of the polyp In any event when other conditions are present specific therapy if possible must be directed toward the cure of these as well as toward the cure of the giardial infection *G lamblia* has been found not infrequently in association with chronic ulcerative colitis but ridding the patient of his giardial infection has failed to cure the chronic ulcerative colitis

TREATMENT

Atabrine is the drug of choice for the treatment of infections with *G lamblia* The dosage is the same as that employed in the treatment of malaria namely

CHAPTER V

GIARDIASIS

Z T BERCOVITZ

SEVERAL INTESTINAL FLAGELLATES HAVE BEEN DESCRIBED but it is not clear which of them definitely cause symptoms The so-called flagellate diarrheas described in some of the older textbooks have been seriously questioned by many authorities One of these flagellates in particular *Giardia lamblia* has been accused of causing dysentery In recent publications some authorities have described numerous symptoms varying widely in nature in patients in whom G *lamblia* has been found On the other hand patients have been seen in whom the presence of G *lamblia* is the only positive finding and *removal of this parasite by adequate treatment has seemed to be followed* by a cure of the diarrheal condition present

CLASSIFICATION OF THE INTESTINAL FLAGELLATES

Class MASTIGOPHORA
  Order PROTOMONADIDA
  Family OCTOMITIDAE
    Genus *Giardia*
      Species *Giardia lamblia*
  Family CHILOMASTIGIDAE
    Genus *Chilomastix*
      Species *Chilomastix mesnili*
  Family TRICHOMONADIDAE
    Genus *Trichomonas*
      Species *Trichomonas hominis*

ETIOLOGY

For a detailed description of G *lamblia* the reader is referred to the chapter on laboratory diagnosis of intestinal protozoa (pages 82 to 84)

EPIDEMIOLOGY

The epidemiology and geographical distribution of G *lamblia* are essentially the same as for other intestinal protozoa G *lamblia* world wide in its distribution occurs in temperate climates with a fair degree of frequency

CHAPTER VI

BALANTIDIASIS

Z T BERCOVITZ

BALANTIDIASIS IS AN INFECTION OF THE HUMAN BOWEL caused by the ciliate protozoan *Balantidium coli* This parasite invades the tissues of the large bowel of man producing ulcerations and symptoms similar to those of amebic dysentery

HISTORICAL NOTE

The first cases of infection with *B coli* were observed in 1857 by Malmsten when the parasite was found in the feces of two patients suffering from dysentery These observations were confirmed by Leuckart in 1861 and by Stein in 1862

ETIOLOGY

B coli is the largest human protozoan parasite that is found in man For a detailed description of the parasite the reader is referred to the chapter on laboratory diagnosis of intestinal protozoa (pages 80 to 8)

EPIDEMIOLOGY

Infection of man results from swallowing food or drink contaminated either by hog or human feces that contain the cysts of *B coli* or by transferring the feces of infected hogs directly to the mouth by the hands The cysts of the parasite are infective and seem to have considerable resistance to external influences They are viable for weeks in hog or human feces especially if kept in the shade in a moist condition but they are killed quite rapidly by direct sunlight and drying

It has been found that cysts of *B coli* remain alive in dry feces in the shade for from one to two weeks but when the feces are exposed to direct sunlight the cysts die within about three hours As a result of numerous experiments it is evident that cysts of *B coli* are much more resistant to drying than those of *E histolytica*

The incidence of infection in man is not great even though *B coli* is a relatively common parasite of the hog

0 1 gm (1½ grains) three times daily after meals for seven days As a rule a single course of therapy is all that is required to rid the patient of his infection In a number of clinics the efficacy of atabrine therapy has been studied by means of gall bladder drainage and specimens of stools obtained following the administration of Epsom salts The results of these observations have shown uniformly that atabrine will rid a patient of *G lamblia* infection

Until the advent of atabrine giardial infections were stubbornly resistant to treatment A great many drugs were suggested but all of them were found wanting Atabrine is universally successful and therefore it is unnecessary to discuss any other form of therapy

INFECTIONS WITH OTHER FLAGELLATES

Other flagellates are found frequently during routine stool examinations but it is impossible to attribute to them any pathologic findings or typical clinical picture Their morphologic characteristics are included as a matter of completeness and for reference purposes



FIG 8 A D g erated *Bal t dia* in abscess just bene th mucos. B Relat v ly normal *B lant d a* n lense conn tive t e ju t above muscularis C *Bala t dium* lesion j t before separation of necrot mucosa (G R Callen ler Courtesy of the *A ch v s of Pathology*)

The *geographical distribution* of *B coli* is extensive human infections having been described in most of the countries of the world

PATHOLOGY

Callender * has given an excellent description of *B coli* which is quoted in the following paragraphs

Balantidium coli is a large free swimming ciliate having both a rotary and a forward movement much like an auger or drill Its cilia are larger than most bacteria It enters the tissue by forcing its way between the gland cells of the mucosa of the colon proceeds between the columnar cells and basement membrane and enters the submucous tissue carrying with it greater or smaller numbers of bacteria Aside from the trauma and secondary infection resulting from its stormy advent the *Balantidium* elicits little response on the part of the host

Macroscopic Appearance Grossly in the well developed case the colon presents numerous shallow blood stained ulcerations with ragged edges and little inflammatory reaction between while the intestinal wall is thickened and indurated

Microscopic Appearance There is not any evidence of a lytic action as seen in *E histolytica* lesions nor a cellular response indicating an inflammatory process when the organism is well embedded in the tissue at a distance from suppuration Characteristically however one sees islands of pus formation surrounding the *Balantidia* in the more superficial locations beneath the epithelium in which the organisms are apparently undergoing degeneration by karyorrhexis (Fig 8A) Here as in infections with *Endamoeba histolytica* the secondary bacterial infection is not favorable to the parasite and they are found only in a morphologically healthy condition at a distance from purulent reaction (Fig 8B) *Balantidium coli* is found in newly formed fibrous tissue laterally and beneath the purulent areas where the fibrosis aids in diminishing the circulation to the overlying mucosa Submucosal abscesses and the fibrosis result in death of the mucosa without its solution and it is then seen as a necrotic layer in which the glands retain their form but nuclei no longer stain (Fig 8C) These necrotic masses appear grossly as opaque pale areas and when sloughed off leave shallow ulcers based on the sclerotic submucous tissue The edges are ragged from strands of mucosa projecting where the necrotic mass separated Small blood vessels are ruptured giving rise to hemorrhage while *Balantidia* in the superficial layers are thrown off and appear in the stool Secondary ulcers are formed by reinvasion from the lumen of the intestine and probably also by extension

Cellular Exudates in Balantidium Coli Infections In the early stages the exudate as would be expected from the foregoing presents a few *Balantidium coli* some of which are degenerated and a few leukocytes The latter show few signs of nuclear change and no evidence of lytic phenomena Soon as the result of secondary infection the number of leukocytes increases until the

* Callender G R *Archives of Pathology* 3 665 1927

CHAPTER VII

COCCIDIOSIS

Z T BERCOVITZ

COCCIDIOSIS IS THE INFECTION OF THE HUMAN INTESTINE by protozoan organisms belonging to the sporozoa order COCCIDIIDA known as coccidia

HISTORICAL NOTE

A coccidium known as *Eimeria gubleri* was reported in 1858 by Gubler In 1860 Kjellberg reported an intestinal infection in man with a coccidium now known as *Isospora hominis* Other species of coccidia were described by Dobel in 1919 but these were not parasites of man

ETIOLOGY

A detailed description of *Isospora hominis* is given in the chapter on laboratory diagnosis of intestinal protozoa (page 89)

GEOGRAPHICAL DISTRIBUTION

According to Magath in 1935 about 208 cases of human infection with *I hominis* had been reported to date Geographically these infections have occurred in the United States Hawaii Brazil Uruguay Argentina the Philippine Islands North and South Africa Morocco Portuguese East Africa West Africa Senegal Nigeria North and Central China Indo China Bengal Dutch East Indies Persia South Russia Italy Egypt Syria Turkey Macedonia Mesopotamia Gallipoli and the eastern Mediterranean region

PATHOLOGY

Nothing is known of the pathology of infections with *I hominis* because the parasite has never been observed at autopsy

SYMPTOMATOLOGY

A mild form of diarrhea with light colored fatty stools has been described Charcot Leyden crystals have been described

TREATMENT

Treatment is of little importance since the disease is of short duration and self limiting in character There is no specific drug for coccidial infections although many of the drugs used in amebic and helminthic infections have been tried

field is practically all pus with the number of *Balantidia* relatively decreased though these organisms are rarely abundant

SYMPTOMATOLOGY

The symptoms produced by *B coli* are indistinguishable from those caused by invasion with *E histolytica* As a rule the symptoms are milder than those of amebic dysentery The picture is usually that of chronic low grade diarrhea associated with moderate gastro-intestinal symptoms pain in the lower abdomen gas slight nausea anorexia and a diarrheal stool containing mucus In some instances the symptoms of acute dysentery with blood and mucus may appear Alternating diarrhea and constipation may be present The clinical picture resembles that of amebiasis so closely that it is impossible to differentiate these two infections

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of *B coli* must be made on the basis of finding the parasites in the bowel evacuations If the patient complains of diarrhea and especially if there is blood or mucus in the stools fecal examinations should be made when the parasites if present will be discovered

The differential diagnosis of balantidiasis includes amebic dysentery giardial diarrhea bacillary dysentery and in fact all the other conditions which cause diarrhea These have been discussed under the differential diagnosis of bacillary dysentery (pages 110 to 113)

PROGNOSIS

The prognosis is usually good especially in symptomless carriers It is not so satisfactory for debilitated individuals who have suffered from diarrheal attacks or other conditions which weaken the system

TREATMENT

There is no specific treatment at present for balantidiasis but excellent results have been obtained with the use of chiniofon given as in amebiasis The course of therapy includes 100 tablets 3 of which are given three times daily (a total of 9 per day for eleven days) Other drugs that have been suggested for treatment of balantidiasis include carbarsone and acetarsone Emetine apparently is useless in balantidiasis High colonic irrigations with silver nitrate quinine and iodine have been suggested and in the opinion of various investigators have met with a degree of success In the experience of the editor *chiniofon* has given excellent results and in addition has occasioned no distress to the patient

PROPHYLAXIS

The prophylactic measures to be employed for balantidiasis are the same as those for amebiasis

The disease is transmitted through fecal contamination of food or through contamination of cooking utensils and food This contamination is more likely to occur where sanitary conditions are poor Direct contagion is an important factor in lunatic asylums and among troops on the march or when soldiers live under field conditions and do not have adequate sanitary facilities In bacillary dysentery the main focus of infection is the latrine

Indirect contagion is attributable to the housefly and possibly to water Houseflies convey the causative agents of the disease by vomiting and defecating previously ingested dysenteric material directly upon articles of diet or upon utensils used in the preparation of food This habit of the housefly seems to be a normal prelude to its feeding Contaminated water is also an important factor in the spread of bacillary dysentery

Carriers of bacillary dysentery are an important etiologic factor and these may be referred to as (*a*) convalescent (*b*) relapsing and (*c*) chronic carriers The carrier state does not as a rule persist for long periods of time The maximum is usually from four to six months although in some cases it has been known to last for three or four years The ordinary chronic carrier gives a history of an acute attack usually with remissions and exacerbations of the disease The excretion of *Shigella* organisms may be intermittent

BACTERIOLOGY

The etiologic agent in bacillary dysentery is one of the organisms in the group of dysentery bacilli which have been placed in the germs *Shigella* and are known as (*a*) *Shigella dysenteriae* (Shiga Kruse) (*b*) *Shigella paradysenteriae* (Flexner Hiss (Y) and Strong) (*c*) *Shigella sonnei* *Shigella ambigua* and *Shigella dispar*

These organisms have been accepted as the causative agents in bacillary dysentery and for their bacteriologic reactions in respect to the various carbohydrates and cultural and serologic reactions the standard texts on bacteriology should be consulted

The *Shigella* group of organisms produces poisonous products known as endotoxins which are found in autolysates and in filtered broth cultures When these are injected into animals the same types of lesions are produced as are encountered in human beings This endotoxin can be neutralized by immune serum It has been shown also that the Shiga type produces a true extracellular toxin against which an antitoxin can be produced

In the human being the etiologic significance of the *Shigella* organisms is shown by their presence in the feces the presence of immune bodies in the serum of infected persons and also by the proved experimental infection of man with pure cultures

Carriers

The real danger in bacillary dysentery comes from the incompletely cured patient or from the convalescent who is still passing mucus in the stools The stools of all such persons should be cultured and their serum should be

CHAPTER VIII

BACILLARY DYSENTERY

Z T BERCOVITZ

BACILLARY DYSENTERY IS AN INFECTIOUS DISEASE OF THE mucosa of the colon and occasionally also of the ileum It is caused by one of the bacillary dysentery group of organisms namely *Shigella dysenteriae* (Shiga *Shigella paradysenteriae*—Hiss Flexner Strong) *Shigella dysenteriae* (Sonne Dispar Ambigua) and is characterized by the passage of frequent blood stained bowel evacuations (stools) or exudate consisting mainly of mixed blood and mucus with little fecal material Pyrexia griping and tenesmus usually accompany these evacuations The patient is toxic rapidly becomes dehydrated and in severe cases coagulation necrosis of the mucosa may take place In milder forms the clinical symptom may be simple diarrhea

HISTORICAL NOTE

In 1898 Shiga discovered the bacillary dysentery bacillus and definitely identified it as the cause of dysentery in 34 of a group of 36 cases that he studied at that time Flexner and Strong in 1900 isolated a bacillus which they believed to be the same as that isolated by Shiga but which later was shown to be slightly different In the United States in 1903 Hiss and Russell isolated organisms from a fatal case of diarrhea in a child which they designated by the letter Y Since then numerous observations and studies have been made on the bacteriology of the dysenteries by such workers as Park who was the first to apply the name Paradysentery to the Park Hiss Flexner and Strong types

Bacillary dysentery has always been a scourge of war It was prominent in the Franco Prussian war of 1871 in the South African war of 1900 and during the World War of 1914–1918 Manson Bahr states that in the Gallipoli Campaign this disease was responsible for the majority of the 120 000 medical casualties evacuated from the Peninsula within three months

ETIOLOGY

Children younger than five years of age are especially liable to contract bacillary dysentery as are those whose resistance has been lowered by chronic and debilitating disease such as malaria the deficiency diseases or other pathologic conditions

This greenish material represents the diseased mucous membrane extending down to the muscularis mucosae layer

The green color is due mainly to staining of dead tissue by bile but partly to the altered blood pigments The intestinal contents as seen in the lumen of the bowel consist of dark grayish fluid containing altered blood but as all the mucous cells have been destroyed comparatively little mucus The necrotic mucous membrane can be scraped off only with difficulty by means of a sharp knife thus revealing numerous small hemorrhages

Nature's cure for this most destructive process consists in exfoliation in much the same manner as in a diphtheritic membrane thus exposing a raw granulating surface Death in this type of dysentery usually takes place at the end of the third week Where the necrotic process affects only limited portions of the bowel ulcers of an irregular outline tend to form Usually they are of an oval or irregular shape and communicate with each other by submucous burrows or sinuses In such cases a mixed infection with *E histolytica* exists This riddled appearance covers the whole of the large bowel

Chronic Bacillary Dysentery Chronic ulceration of the large bowel is the outstanding feature of chronic bacillary dysentery Apparently the lesions are at first small and consist of tiny lenticular ulcerations of the surface involving the mucosa alone sometimes they occur in the lower part of the ileum as well The ulcers are irregular in shape (Fig 9) and run at right angles to the long axis of the bowel the edges are not undermined and the base consists of a grayish or brownish slough in chronic bacillary dysentery sometimes pseudopolypoid formation takes place and the swelling of the mucous membrane is so intense that the lumen may be occluded

Perforation of the bowel as a result of bacillary dysentery may take place although it is a very rare event as compared with the frequency with which it has been noted in chronic amebiasis



Fig 9 Colon in bacillary dysentery (Courtesy of U S Army Medical Museum)

Retention Cysts and Polypoid Formation A curious pathologic condition—the direct sequela

examined for evidence of agglutinins All cases are suspicious which have a positive reaction or a titer of 1 25 for dysentery organisms

PATHOLOGY

Mild Bacillary Dysentery The earliest lesions originate in the lymphoid follicles of the large intestine These becoming infected give rise to superficial snail track ulcers which travel across the bowel spreading the free edges of the transverse folds of the mucosa there is concurrent catarrhal inflammation of the mucous membrane with the secretion of much viscid mucus

Acute Bacillary Dysentery In these cases there is acute hyperemia of the large intestine which eventually results in a gangrenous process of the whole of the mucous membrane This is especially so in the lower portions of the large intestine but it may affect the last eight feet of the ileum and very exceptionally the whole of the small intestine The process is especially severe in the rectum and pelvic colon the cecum and the hepatic and splenic flexures appear to be particularly involved This acute inflammation and necrosis is brought about by direct action of the dysenteric toxin on the cells of the mucous membrane and possibly also by its elimination from the blood stream In especially virulent cases death may take place in as short a time as fifty six hours after the onset of the disease

At autopsy the appearance of the cadaver suggests an intense degree of toxemia but there is no wasting There is paralytic distention of the large intestine the mucosa is bright scarlet red very friable and dripping with blood but there is no actual infiltration of the walls of the intestinal canal The lumen of the bowel is filled with viscid mucus intermingled with blood in the small intestine there is similar out pouring tinged green with bile Abundant signs of a widespread absorption of toxin are usually found Thus general lymphoid peritonitis is present with exudation of free serous fluid into the peritoneal cavity lymphoid flocculi of the peritoneal surface and edema of the mesentery The mesenteric glands are enlarged red and soft

In less acute cases which do not run such a rapid fulminating course the mucous membrane appears a rosy plum color mottled with numerous sub mucous hemorrhages while the whole bowel is edematous and consequently much thicker than normal From the numerous extravasations of blood into the submucosa one is justified in referring to this variety as the acute hemorrhagic type of bacillary dysentery

In those who survive the dysenteric process for more than a week the stage of coagulation necrosis is reached At this period the cadaver shows very considerable signs of wasting The large intestine especially the sigmoid flexure is in a spastic condition and is narrowed down to a small tube The bowel wall is thickened by edema hemorrhages and cellular infiltration The appendices epiploicae are engorged discolored and even edematous The mucous membrane is converted into an olive green brownish or even blackish substance which is rigid to the touch and pitted on the surface like a consolidated lava field The last few feet of the ileum may be similarly affected



Fig o Exud tes of bac ll ry dy ntery (A B) compared w th exud tes of amebic dysentery (C D) A an l B methylene blue v et p eparat o × 9/o and D Schaud nn s fi tion Heiden ha n iro i hematoxyl n sta n C × 430 D ×) o (Berco tz *An ls of Intern l Med cine*)

of chronic bacillary dysentery and frequently seen in autopsies on natives of the Eastern countries—is *the formation of tapioca like mucous retention cysts* which vary in size from that of a hemp seed to that of a cherry which are distributed unequally through the large intestines causing excrescences on the peritoneal surface from which on incision a clear jelly like mucus can be expressed The retained material which is often infected with Flexner bacilli and with *Escherichia coli* may result in abscess formation within the bowel wall These cysts form through proliferation of the mucous membrane beneath the muscularis and their presence explains the occurrence of that type of intractable mucous colitis which is frequently a sequela of genuine bacillary dysentery and difficult to treat Repair of chronic ulceration takes place extremely slowly by the formation of pigmented scars which are visible as bluish depressions beneath these scars retention cysts frequently form

HISTOPATHOLOGY

In the acute stages the mucous membrane becomes invaded with inflammatory cells mostly of the plasma cell type the capillaries are engorged and there are numerous small hemorrhages while the mucus secreting cells are *enlarged and stimulated to excessive action In the submucosa there is engorge*ment of the veins with considerable accumulations of inflammatory cells in the submucous tissue The inflammatory changes are most intense in the vicinity of the lymphoid follicles situated beneath the mucosa

In the necrotic stage the crypts of Lieberkuhn s follicles are for the most part destroyed so that no definite structure can be distinguished this layer has undergone coagulation necrosis and is converted into a dense structure in which small hemorrhages accumulations of leukocytes and pyknotic nuclei are visible The muscular fibers can be demonstrated The submucosa is thickened to two or three times its normal width it is distended with inflammatory edema and is the seat of numerous hemorrhages The chief features are thrombosis and the destruction of the blood vessels especially the veins In the capillaries it is possible by appropriate staining to recognize large macrophage endothelial cells apparently derived from the capillary endothelium They are often of a large size from 15 to 20 microns in diameter and contain ingested red blood cells and sometimes leukocytes when seen in the stools of bacillary dysentery they are liable to give rise to confusion as they bear a close resemblance to the dysentery ameba In these severe cases the muscular fibers of the circular and longitudinal muscular coats stain badly and are adversely affected by toxic changes Cases have been seen in which all the layers of the bowel wall have undergone this process of coagulation necrosis

CYTOLOGY OF THE EXUDATE

The following description of the exudate is quoted from Callender (1937)

The cytology of the exudate follows (Fig 10) the pathology which produces it After the feculent content of the bowel has been eliminated the exudate is of thin seromucus and contains young leucocytes with ringed nuclei red

In the diphtheritic type pseudomembrane is formed as in diphtheria Its removal by a swab leaves a ragged bleeding surface Later masses of the membrane slough and the endoscope shows a shaggy pus bathed grayish red surface often with relatively long strings of membrane pendant in the bowel lumen When this membrane sloughs the entire bowel may be lined by granulations but usually islands of mucosa less involved in the necrosis are left as foci from which regeneration occurs

In the milder non-diphtheritic cases superficial ulcers occur appearing at first as very tiny raised points usually with an opaque yellowish apex They spread rapidly at the periphery and soon coalesce presenting denuded areas of varying size and shape The lesions do not increase rapidly in depth but progress peripherally The muscular layers become spastic and very irritable The lumen beyond the sigmoidoscope frequently presents the appearance of a tunnel fixed in outline by the spastic muscular layers twitching in irritable reaction to slight manipulation The wall oozes blood the surface contributes necrotic epithelium The picture is unmistakable

SYMPTOMATOLOGY

Cases of bacillary dysentery may be divided into mild acute and fulminating infections In addition to these there are also patients who have been in one of these groups but who have suffered a relapse or in whom the disease has become chronic

Mild Bacillary Dysentery The Flexner group of organisms usually causes mild infections the constitutional symptoms of which are not severe Fever may be present and the bowel movements which may be diarrheal from the onset contain a certain amount of blood and mucus The prostration fever straining tenesmus and griping that accompany such an attack of bacillary dysentery are relatively mild

Acute Bacillary Dysentery The onset of an attack of bacillary dysentery in about 80 per cent of cases is sudden and marked by rigors fever headache vomiting and diarrhea

The onset of symptoms follows a short *incubation period* which may be less than forty-eight hours or as long as seven days In experimental laboratory infections it is usually about three days The onset is almost invariably dramatic starting suddenly with abdominal pain and colic These symptoms are accompanied by violent tenesmus and diarrhea The main clinical symptoms include inflammation of the large bowel with griping tenesmus passage of loose scanty blood stained mucous discharges that are often devoid of fecal matter The nearer the lesions are to the rectum the more urgent is the tenesmus while if the inflammatory condition is nearer the cecum there is usually griping The frequent bloody stools and the abdominal pain are accompanied by great prostration The number of stools may reach as many as thirty or forty a day for short periods except in acutely toxic cases in which there may not be much change in the number or character of the stools The general constitutional symptoms which may be very marked are usually due

corpuscles and macrophages Many of the latter contain remnants of the other cellular elements Both leucocytes and macrophages show karyorrhexis and may appear as cell membranes within which are chromatin remnants and nonstaining detritus These are the results of toxic degeneration and are called ghost cells The bacterial content decreases and soon becomes very scanty Blood at first is present as scattered corpuscles but gradually increases until the exudate is blood streaked to naked eye examination although there is rarely a frankly bloody stool as seen in some cases of amebic dysentery As ulceration progresses the exudate becomes more and more purulent Macro phages decrease and the leucocytes show degenerative changes and aging as in abscesses Extensions of the process to new areas in the mucosa may cause an increase in young leucocytes and macrophages Such a picture is caused by a spreading of the process to hitherto uninvolved areas and calls for further serum therapy Sufficient serum given early may avoid the frankly purulent stage

Healing is indicated by a decrease in the quantity of exudate and in the proportion of young leucocytes Older cells show an even staining of the nu clear masses and many are distorted in shape or broken up The mucus be comes thicker tenacious and forms tough shreds which retain nuclear dyes Enmeshed in this mucus are degenerated epithelium leucocytes often in masses and numerous bacteria The final picture often seen only in exudate adherent to formed feces consists of strings of mucus containing leucocytic remnants and groups of epithelial cells scraped from partially healed ulcera tions This stage may not be seen if care is taken to keep the feces from be coming hard or scybalous

Pus with or without blood may appear in the feces in other conditions than dysentery as ulcerated diverticula tuberculous or syphilitic ulceration lymphogranuloma of the rectum malignant disease and from abscesses empty ing spontaneously into the intestine The clinical symptoms of acute dysentery are rarely present though those of the chronic form may be simulated The bacterial content is high No macrophages are seen and usually a larger pro portion of the leucocytes are degenerated In cancer masses of more or less degenerated atypical cells may be found

SIGMOIDOSCOPIC APPEARANCE OF THE BOWEL

The sigmoidoscopic appearance of the bowel has been described by Cal lender on the basis of a large series of cases The appearance of the bowel early in bacillary dysentery is that of a generalized inflammatory reaction There may be some variation in intensity but the entire mucosa is involved There is first a hyperemia acute in nature and not unlike the appearance of nasal mucosa in acute coryza This appearance does not remain unchanged for long Within a few hours there is added to the increasing hyperemia an edema which gives the bowel wall an appearance of increased thickness Exfoliation of the superficial layers of the mucosa may be observed and the wall is bathed in blood pus and necrotic epithelium (Plate XI)

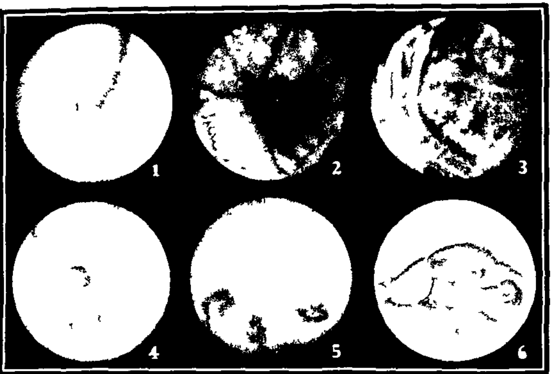


PLATE XI

PLATE XI

SIGMOIDOSCOPIC APPEARANCE OF THE BOWEL

1 Normal bowel—rectosigmoid fold

2 Stricture of rectum following chronic ulcerative colitis Note hemorrhages from edematous friable mucosa following attempts to enter stricture with sigmoidoscope

3 Chronic ulcerative colitis with streaks of mucus still adherent

4 Polyp of the sigmoid as seen from just below the rectosigmoid fold

5 Single ulcers of the rectum—traumatic due to patient s finger nail Note the moderate degree of atrophy of mucosa with capillaries showing through the thin membrane

6 Multiple polyposis in a patient with lymphogranuloma venereum with positive Frei test

(From Bercovitz and Fuller *American Journal of Digestive Diseases* 1940)

picture caused by this bacillus is not as clear cut as that of the Shiga and Flexner infections In some instances the symptoms approximate those of acute Flexner dysentery with the sudden onset of illness diarrhea colic and the appearance of blood and mucus in the stools These symptoms may be relatively mild or acute when acute they include vomiting diarrhea and the passage of stools resembling the choleraic form of Shiga dysentery together with rapid prostration In most of the Sonne infections there is a tendency for fever to be associated with the abrupt onset but in some instances the fever is slight and transient A curious feature of Sonne dysentery is the respiratory picture generally a mild respiratory catarrh that not infrequently precedes the development of the abdominal symptoms

Choleraic Bacillary Dysentery The choleraic form of bacillary dysentery is fortunately rare but it must be recognized because of its resemblance to cholera The onset is acute and the symptoms include vomiting and collapse The face is pinched eyes sunken temperature subnormal tongue dry and glazed the skin of the extremities cool and clammy The pulse is small thready and rapid Death takes place within three days of the onset

Gangrenous Bacillary Dysentery The gangrenous form also begins suddenly but the temperature rises rapidly the face is flushed feverish and the pulse is rapid and bounding Severe abdominal pain and tenesmus are characteristic of this type of bacillary dysentery

Relapsed Cases of Bacillary Dysentery Some bacillary dysentery patients apparently improve under appropriate therapy but after a time they undergo a relapse The stools may recover their fecal character or may even become mushy and show some evidences of formation They continue however to be passed too frequently and to contain a variable amount of mucus and pus

Chronic Bacillary Dysentery Chronic bacillary dysentery follows in the wake of the acute forms in patients who are not completely cured of the initial attacks but continue to have frequent evacuations of fecal matter blood mucus and pus Many of these patients develop chronic ulcerative colitis

Bacillary Dysentery in Children In the tropics children under five years of age are particularly subject to bacillary dysentery The disease is always very serious when it attacks young children As a rule it is more severe in European or American children than in natives It is now recognized that many of the epidemics of so called summer diarrhea in children are in reality outbreaks of bacillary dysentery

Residual Symptoms The most important residual symptoms in bacillary dysentery are those of chronic ulcerative colitis frequent passage of blood mucus and pus with intervals of fever accompanying exacerbations and remissions of the bacillary dysentery The patient shows marked signs of wasting and of mental depression Finally he becomes weak or if he is able to maintain a fair state of nutrition in spite of the fever and diarrhea that accompany the disease he may be subject to stricture of the rectum or to perforation of the bowel both of which involve peritonitis and usually result in death

to the absorption of toxins The acutely toxic cases may terminate in death of the patient

The character of the stools is typical of the disease At first they may contain a small amount of fecal matter and be diarrheal in character Their nature changes very rapidly They soon become free of fecal matter and consist of viscid blood stained mucus that is thick sticky and small in amount During the first few days the blood stained mucus adheres to the bed pan sometimes it is practically odorless at others it may have a faint musty odor In the most acute and fulminating stage of the disease the stools contain a large proportion of dark and decomposed blood that has been compared to meat washings The stools may consist of blood clots with a background of green bile stained mucus *In the very rapidly fatal cases neither blood nor mucus may* be noticed at the start but a foul fluid mass containing much altered blood without the mixture of mucus is passed

Tenesmus Tenesmus is one of the most important features of the disease The patient strains constantly to evacuate the bowels but is unable to pass more than a very small amount of bloody mucus The straining is so constant that it weakens the patient and prevents his obtaining adequate rest

Fever The temperature which may have been preceded by a chill usually rises very rapidly and may reach from 39 to 39 5 C (102 2 to 103 1 F) Within a week or more as the urgency of the symptoms disappears the temperature gradually returns to normal On the other hand some patients with bacillary dysentery do not have fever

Abdominal Pain Abdominal pain is an important symptom and is usually griping and generalized in character At times it is difficult to separate abdominal pain and tenderness from the tenesmus with which they may go hand in hand Spasm of the rectum together with these symptoms may last for one half hour after the passage of the stools or it may be continuous

Palpation of the Abdomen This usually causes distress and elicits signs of tenderness As a rule palpation is difficult because of spasm of the recti muscles In the most serious toxic cases in which the prognosis is serious the pain passes off and sensation is blunted by toxic absorption The transverse colon and cecum cannot be palpated as readily in bacillary dysentery as they can in amebic dysentery

Fulminating Bacillary Dysentery Cases of fulminating bacillary dysentery will be seen under epidemic conditions or in isolated instances The symptoms of acute bacillary dysentery are aggravated The attack usually begins with chills temperature which may reach 40 C (104 F) nausea vomiting and headache Shortly afterward purging begins In from two or three days to a week collapse may set in the temperature then becomes subnormal and death may result from toxemia In such cases the abdomen is sunken and acutely tender The stools are liquid offensive and greenish or gray in color they may be too numerous to count

Sonne Dysentery The Sonne dysentery organism apparently gives rise to a group of symptoms which are characteristic of bacillary dysentery The clinical

Bacillary Dysentery	Amebic Dysentery
Death due to (*a*) exhaustion (*b*) toxemia	Death due to (*a*) exhaustion (*b*) perforation of bowel (*c*) hemorrhage (*d*) liver abscess
Signs Generalized tenderness over abdomen usually more intense over sigmoid colon	Signs Local tenderness and thickening mostly over sigmoid flexure transverse colon and cecum
Tenesmus Very severe	Tenesmus Usually not present
Emaciation Almost invariable	Emaciation Uncommon
Pathology Acute diffuse necrosis of mucous membrane of the large intestine	Pathology Local lesions confined solely to large intestine due to characteristic ulcers
Ulcers When present situated on free edge of folds of mucous membrane distributed transversely to long axis of the bowel Ulcers are usually serpiginous in outline with ragged undermined margins, often intercommunicating Bases consist of granulation tissue no compensatory hypertrophy of the bowel wall Intervening mucous membrane chronically inflamed	Ulcers Bouton de chemise —commence as small abscesses of submucosa distributed in the long axis of the bowel Ulcers oval in shape regular in outline flask shaped Infection involving all coats of the bowel Bases usually consist of dark necrotic Dyak hair sloughs Ulcers perforate not uncommonly compensatory hypertrophy of bowel wall Intervening mucous membrane quite healthy
Stools Small in amount numerous bright red blood gelatinous viscid odorless resembling red currant jelly	Stools Feces intermingled with blood and mucous Sago-grain stool or sometimes anchovy sauce Copious in amount and usually very offensive
Reaction Alkaline	Reaction Acid
Microscopic Numerous red cells and polymorphonuclear pus cells Macrophage inflammatory cells Few bacilli visible	Microscopic Red cells numerous and in rouleaux Polymorph cells much damaged with extruded nuclei Macrophage cells absent Large numbers of motile bacilli Active *Endamoeba histolytica* with ingested red cells Charcot Leyden crystals common
Blood Examination No leukocytosis	Blood examination Moderate leukocytosis
Serum agglutination Usually serum agglutinates one or other dysentery bacilli	Serum agglutination Negative
Therapeutic test No reaction to emetine	Therapeutic test Almost immediate reaction to emetine
Sigmoidoscopy Granulation tissue and rigidity of bowel wall Usually no ulcers visible	Sigmoidoscopy Lax and redundant mucous membrane Small ulcerations with hemorrhagic margins

COMPLICATIONS

The complications of bacillary dysentery are primarily the arthritic manifestations known as dysenteric rheumatism Not infrequently there is swelling of the knee or ankle either during the acute stage of the disease or more commonly during convalescence when the stools are less frequent The arthritic complications are *more common in the Shiga infections As a rule fever* is present The condition seems to clear up after a long time without leaving permanent deformity although in some cases permanent disability may result *Acute conjunctivitis* and *iridocyclitis* are frequently noted complications and may be present with arthritis *Parotitis* is a not uncommon complication *Prolapse of the bowel* due to severe straining is a frequent complication especially in severe cases among children

Sequelae are essentially chronic ulcerative colitis stenosis of the large bowel peripheral neuritis and achlorhydria

DIAGNOSIS

Bacillary dysentery should be considered as a probable diagnosis in all cases of diarrhea It may be suspected if microscopic examination of the bowel discharges reveals the presence of a heavy cellular exudate with a predominance *of polymorphonuclear leukocytes showing toxic and swollen cells with ringed* nuclei The microscopic picture also shows the presence of macrophage and epithelial cells that may contain toxic granules The final diagnosis of course must depend on the demonstration of one of the organisms of the bacillary dysentery group and on positive blood agglutination reactions

DIFFERENTIAL DIAGNOSIS

The *differential diagnosis includes all other conditions in which* diarrhea may be a symptom

Amebic dysentery is characterized by a relatively insidious onset but without the severe toxemia associated with bacillary dysentery Manson Bahr (1939) has tabulated the differential diagnosis in bacillary and amebic dysentery as follows

Bacillary Dysentery	Amebic Dysentery
Lying down dysentery	Walking dysentery
An acute disease with tendency to epidemic spread	A chronic endemic disease
Incubation period short seven days or even less	Incubation period in man a lengthy one —at least fourteen to ninety days may be longer
Onset Acute	Onset Insidious
Pyrexia Common	Pyrexia Rare unless complicated
Complications No hepatitis polyarthritis frequent and occasionally iridocyclitis	Complications Hepatitis hepatic amebiasis amebic abscess

ditions to be considered are schistosome infections oesophagostomiasis heterophyaisis fasciolopsiasis and strongylodiasis

Diarrheas are sometimes associated with typhoid partyphoid and Salmonella infections and of course cholera is always prominent in the consideration of any acute diarrheal condition Associated with sprue are the so-called idiopathic steatorrhea celiac disease and pancreatogenous steattorrhea Diarrheal conditions are frequently associated with poisonings with mercury uremic conditions and other forms of toxic colitis including thyrotoxicosis Other diseases in which diarrhea is a symptom but not so frequently seen include actinomycosis tuberculosis syphilis diverticulitis intussusception hemorrhoids and foreign bodies in the rectum

PROGNOSIS

The prognosis in bacillary dysentery depends on the degree of infection as well as on the virulence of the organisms present In severe infections in the very young or the aged or in patients suffering from some intercurrent disease the prognosis is usually bad or at best it must be guarded Bacillary dysentery may be a terminal infection in other diseases

In chronic infections especially of the Flexner type the prognosis for life is fair as far as the immediate outcome is concerned but the prognosis for cure must of necessity be very guarded especially in cases in which chronic ulcerative colitis develops Patients suffering from chronic or recurring attacks of dysentery are useless in the army

TREATMENT

The treatment of bacillary dysentery is (a) specific and (b) supportive

Specific Therapy

Polyvalent antiserum may be administered in large doses As the serum is usually obtained from the horse it is essential to determine the patient s sensitivity to it before it is administered But even with this precaution in many cases a severe serum reaction may follow immediately or later since to obtain satisfactory results it is necessary to use about 80 to 100 cc of polyvalent serum The *serum may be given intramuscularly or intravenously but when* the latter method is used it should be given very slowly or mixed with saline and administered by the drop method In any event the danger of serum reaction is very great

Sodium sulphate or ***magnesium sulphate*** administered in the form of crystals is almost specific and has the advantage that there is no serum reaction to follow This method of therapy has been established for well over a hundred years and has not only stood the test of time but has also won the approval of many competent observers throughout the world

Sodium sulphate is administered to adults usually in doses of one tablespoonful It may be given as a single morning dose or it may be given in divided doses throughout the day Within twenty four hours after the administration of sodium sulphate or magnesium sulphate it will be noticed

Chronic ulcerative colitis is a disease condition involving the large bowel Its onset may be either acute or slow and insidious and is accompanied by frequent movement of the bowels The stools are characterized by the presence of blood mucus and pus Some cases of chronic ulcerative colitis seem to fol low in the wake of an acute attack of bacillary dysentery but there are many others in which the etiologic factor cannot be adequately determined The diagnosis is usually confirmed by sigmoidoscopic examination and roentgen ray examination with the barium colon enema

Carcinoma of the rectum and sigmoid is frequently attended by sudden onset of blood stained diarrhea Reliance must be placed on sigmoidoscopic examination and microscopic studies of the bowel discharges The diagnosis should be confirmed by a biopsy Very small masses in the rectum or sigmoid *of female patients must be differentiated from endometrial transplants associ* ated with endometriosis That carcinoma of the rectum or sigmoid has to be seriously considered in every case of diarrhea is exemplified by the fact that in some cases *E histolytica* parasites or some other protozoa such as *B coli* or *G lamblia* are found in addition to the carcinoma Eradication of the para sites by appropriate treatment in such cases fails to clear up the condition The symptoms should then be carefully re evaluated the stools should be re examined and there should also be sigmoidoscopic and barium colon enema studies with the roentgen ray

Carcinoma of other areas of the bowel as well as terminal ileitis must be taken into account These conditions may usually be diagnosed with the aid of the roentgen ray examination

Lymphogranuloma venereum involving the rectum is caused by a specific *virus It is a condition that is also accompanied by discharge of blood stained* mucus from the rectum The diagnosis should be confirmed by the Frei test which has been described in the discussion of Lymphogranuloma Venereum (page 503) Inguinal adenitis or involvement of the vulvae may also be pres ent with lymphogranuloma venereum

Sprue is a diarrheal condition that occurs frequently in the tropics It is characterized by a morning diarrhea The evacuations are copious exceedingly foul in odor shot through with gas and oily in character Other signs of sprue are the typical beefy smooth tongue achlorhydria a flat glucose tol erance curve following administration of glucose by mouth and a normal glucose tolerance curve when the glucose is given intravenously The sprue picture is usually completed by the presence of a macrocytic type of anemia with a relatively high color index

Malarial dysentery is caused by the plugging of the capillaries of the bowel with the developmental forms of *Plasmodium falciparum* and is usually ac companied by chills fever and blood stained diarrhea especially in persons who have had previous infections with this plasmodium

Other conditions to be considered in differential diagnosis include other protozoal dysenteries such as *B coli G lamblia* other intestinal flagellate and leishmanial infections and intestinal coccidiosis Among the helminthic con

The method of preparation of plasma has been discussed under the treatment of typhoid fever (page 559)

Dietary Measures Patients with bacillary dysentery should have a high protein low residue and high vitamin diet Enough starches should be added however to maintain the patient s caloric requirements Scraped chopped beef which may be given twice a day is indicated The patient s strength can be maintained better under this regimen than if gruels and starchy substances only are given under the false impression that food in the stomach causes diarrhea Milk should not be given although buttermilk is acceptable Puréed vegetables are indicated and the list should include green vegetables with the exception of gas forming vegetables such as onions and the like Fruits and fruit juices are acceptable to these patients Following is a suggested diet schedule for use of the patient

SPECIAL DIET LIST

Important Note Read and Follow Exactly

1 The object of this diet is to provide foods which will be easily digested readily absorbed and leave a minimum of residue that might be irritating to the bowel

2 Your absolute co-operation in the matter of diet is vital in the proper handling of your condition

3 Make no changes without consultation *Eat only the foods listed below*

4 Please bring this diet list with you at each office visit

5 Eat some of the following food at 10 A M and 4 P M and at bedtime Bouillon chocolate flavored vitavose (Squibb) eggnog fruit juice Holland rusk toasted white bread zweiback

Only the Foods Listed Below May Be Eaten

Beverages	Bovril cocoa coffee cream milk malted milk buttermilk weak tea vegex vichy (Fruit juices as listed)
Bread stuffs	Bread sticks dry white toast Holland rusk melba toast zweiback
Cereals	Cream of wheat farina hominy strained oatmeal
Desserts	Cornstarch pudding custards D zerto ice cream (without nuts or seeds) jello junkets Knox gelatin Royal pudding
Eggs	Poached soft boiled scrambled in double boiler or used in eggnogs or custards
Fruits	Puréed or canned grapefruit (canned or fresh without membrane) peaches pears bananas
Fruit Juice	Grapefruit juice orange juice pineapple juice tomato juice lemon juice with sugar
Meats	Lean bacon roast beef pot roast boiled beef scraped chopped beef heart (calves beef lamb) broiled lamb chops roast lamb broiled or boiled filet of sole boiled tongue boiled ham calves liver and chicken
Soups	Bouillon half milk and half cream with addition of puréed vegetables strained vegetable soup in which no onion or other gas forming vegetable has been cooked (made from only vegetables listed below) lentils and split pea
Starches	Baked potato without the skin mashed or other soft forms of potato rice well cooked with plenty of water until soft macaroni and spaghetti
Vegetables	*All to be puréed* Asparagus beets beet greens carrots peas spinach squash string beans swiss chard broccoli

that the stool becomes more copious that there is less straining and tenesmus and that the general condition of the patient shows improvement A table spoonful of the salts should be continued for two days after which the dose may be decreased to three teaspoonfuls for two or three days then two tea spoonfuls and finally one teaspoonful By this time it will be noticed that the stools are soft mushy and feculent in character and that practically all the blood and pus will have disappeared

Chemotherapy The action of sulfanilylguanidine on the *Shigella dysenteriae* group of organisms has recently been studied A number of observers found this drug to be effective against these organisms The drug is relatively non toxic The dosage used at present is 0 10 gm per kg of body weight as the initial dose followed by 0 05 gm per kg every four hours until the stools become four a day or less after that 0 10 gm per kg every eight hours is given for another three or four days The course of treatment with this drug should never exceed fourteen days and a daily blood count and urine examination should be made If the blood count cannot be made each day at least a speci men of urine should be examined to ascertain whether there is the heavy precipitation of crystals which occurs frequently in patients receiving the drug This seems to be transitory and disappears quickly when the drug is stopped and fluids are administered in large quantities The real evaluation of this and other drugs in this group can be made only after a period of at least five years during which a large number of patients have been carefully observed by different workers in the field

Other chemotherapeutic agents have been suggested from time to time and all have some virtue but so far it is impossible to speak of a true specific thera peutic agent which has been of value in all cases Chiniofon (anayodin) given either by mouth or as a retention enema has been found of value in some in stances Silver nitrate Dakin s solution tannic acid animal charcoal with or without kaolin and even rivanol and salol have had adherents In any event whatever measures are employed it is important to consider the general physi cal condition of the patient

General Supportive Measures

Glucose Infusions Five per cent glucose in normal saline is administered intravenously and may be given in amounts of from 2 000 to 3 000 cc daily depending on the physique weight and size of the patient

Blood Transfusions Early in the treatment of bacillary dysentery blood transfusions should be given Whole blood is probably the best therapeutic measure we have at our command today Every three or four days 500 cc should be administered to the patient by the direct method The blood and the glucose in normal saline can be administered together in the course of treatment

Plasma Transfusions These may be given daily or every other day as re quired by the condition of the patient Plasma has the added advantage that it can be used where proper typing facilities are not available The plasma may be given either before or after an infusion with glucose in normal saline

In recent practice methods have been devised that eliminate much of the drain upon the patient's vitality and consequently enable him to obtain as much rest as possible Instead of the constant use of the bed pan it has become customary to use a sort of diaper with absorbent cellulose composition pads The patient is encouraged to allow the bowels to evacuate into this diaper and is told that it has been devised to save his strength as much as possible

It may be well to call attention to the effect which straining to move the bowels has on the bowel mucosa It is a common observation and can be easily demonstrated through the sigmoidoscope that when a patient with a normal (pale pink soft velvety) bowel mucosa strains redness swelling and edema immediately develops and in some cases the bowel has been seen to bleed while it is under observation As soon as the patient relaxes these abnormal conditions recede It requires no stretch of the imagination to see the effect which constant straining and tenesmus have on the unfortunate victim of bacillary dysentery This also applies to the patient with chronic ulcerative colitis

PROPHYLAXIS

Personal prophylaxis is of the greatest importance in bacillary dysentery Particular attention must be paid to food and drink During an epidemic no food or drink should be taken that has not been thoroughly boiled and protected against subsequent contamination Water should be carefully protected after it has been sterilized by boiling Milk is one of the chief media for the spreading of bacillary dysentery It may be contaminated by the vessel in which it is stored as a result of contact with infected water or with the feces or infected flies

All dishes in which food is stored as well as dishes and cutlery used at table should be carefully sterilized and protected from flies and dust Flies constitute one of the most serious dangers and their breeding grounds which include manure heaps garbage and latrines should receive special attention

The care of the hands is also of great importance in personal prophylaxis Hands should be carefully washed before food for human consumption is touched

Vaccination and Bacteriophage

The problem of vaccination against bacillary dysentery has been studied for many years but so far a satisfactory vaccine has not been developed A large literature has accumulated regarding the use of bacteriophage as a preventive measure and experience in Brazil Egypt Russia France and Germany indicates that the morbidity from dysentery can be reduced by the oral administration of polyvalent dysentery bacteriophage whenever an outbreak begins Oral administration of bacteriophage is simple harmless and may be of value There is no contraindication to giving polyvalent bacteriophage as a dysentery prophylactic in the face of an epidemic outbreak of bacillary dysentery

Do Not Take the Following

Alcohol	Alcohol in any form (including medications containing alcohol)
Cathartics	Cathartics or laxatives in any form
Meats	Cured meats fried meats corned beef dried beef ham kidney pork shellfish or veal
Pastry	Rich pastries
Spice	Highly spiced or highly seasoned foods
Vegetables	Vegetables which have not been puréed artichoke brussel sprouts cabbage cauliflower corn cucumbers *lettuce* lima beans onions peppers radishes sauerkraut scallions *tomatoes* turnips watercress

It is often desirable to give the patient nourishment between meals A nourishing drink may be made as follows Whip one tablespoonful of malted milk powder into about 3 or 4 ounces of water beat in one or two eggs when the powder is thoroughly mixed and serve with a scoop of vanilla ice cream Another means of giving light nourishment is by adding 2 or 3 ounces of pressed beef juice to beef broth This should be served either clear or else with some well cooked rice

Tomato juice may be given with one meal It should be taken with food and not on an empty stomach It should first be given in tablespoonful amounts and increased until 2 or 3 ounces are taken with each meal Given in this way many patients are able to tolerate tomato juice whereas they could not manage it given in a large quantity on an empty stomach Orange juice is more likely to cause distress than tomato juice

Sedation In bacillary dysentery rest is of vital importance to the patient Codeine in full dosage morphine or pantopon may be administered Phenobarbital to which sodium bromide and possibly some tincture of belladonna have been added is valuable if the patient is suffering unduly One favorite prescription is as follows

℞ Tincture belladonna	8 0 cc
Sodium bromide	10 0 cc
Elixir phenobarbital qs ad	60 0 cc
M Sig Take one teaspoonful every 4 hours	

Paregoric is of doubtful value in bacillary dysentery While no harm will result from its use it rarely does good when there is a definite breakdown in the bowel mucosa For severe tenesmus a suppository made up as follows is helpful

℞ *Epinephrin 1 100*	*3 0 cc*
Anesthesin	3 0 cc
Cocoa butter qs ad	0 0 cc
M Fiat Suppositories No X	
Sig One every 4 hours as needed	

If these measures fail to give the patient sufficient rest morphine is indicated It is good therapy to use morphine under such conditions because rest and quiet sleep are most valuable to the patient

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CHAPTER IX

CHOLERA

JOSEPH F SILER

CHOLERA IS AN ACUTE SPECIFIC INFECTIOUS DISEASE caused by the *Vibrio cholerae* or so-called comma bacillus In the initial stage it is usually characterized by the sudden onset of copious and painless watery stools the color of rice water and by vomiting of large amounts of watery fluid The stage of evacuation merges into the stage of collapse due partly to toxemia and partly to loss of fluids Collapse is manifested by cold clammy shriveled skin (washerwoman s hands) surface temperature below normal violent and painful cramps of the muscles of the extremities and abdomen suppression of urine shallow respiration and poor heart action If through natural resistance or the application of modern methods of treatment the patient survives this period of collapse the stage of reaction follows in which the normal body functions are restored—the diarrhea ceases the stools become normal in character kidney function becomes normal fluid is restored to the blood and tissues of the body the temperature of the body surface rises to normal and heart action becomes normal Convalescence following the stage of reaction is usually rapid

HISTORY AND GEOGRAPHICAL DISTRIBUTION

Available records indicate that cholera has been endemic in oriental countries particularly in India and probably in China for many centuries and that epidemics have occurred with unfailing regularity in its areas of endemicity From these endemic areas the disease has been spread by human intercourse along routes of communication (land and sea) causing widespread epidemics in India China and elsewhere in the Orient and at times extending in pandemic proportions to European countries Africa and the Western Hemisphere

It is not feasible within the scope of this discussion to review in detail the history and geographical distribution of cholera Those who are interested in this phase of the subject are referred to the excellent reviews appearing in Tropical Medicine by Rogers and Megaw and Scott s History of Tropical Medicine

EPIDEMIOLOGY AND ETIOLOGY

Prior to about the middle of the nineteenth century many conflicting views were held concerning the causation and method of spread of cholera though it was recognized that the infected individual routes of communication and water supplies must of necessity be connected in some manner with the dissemination of the disease

By the later years of the nineteenth century it had become apparent that intercourse between human beings was the primary and most important factor in the dissemination of cholera

In 1883 the specific etiologic agent *V cholerae* was discovered by Koch Koch headed a German cholera commission that investigated cholera during an epidemic in Alexandria Egypt in the latter part of 1883 A characteristic bacillus—the comma bacillus—was recovered from the walls of the intestine of cholera cases at autopsies The commission transferred its activities to Calcutta India in 1884 and was able to confirm its previous findings by examinations of tissues and cultures from autopsy material and by microscopic examinations and cultures of stools from cases of cholera

METHODS OF IDENTIFICATION OF THE VIBRIO CHOLERAE

The *V cholerae* that is usually observed is a short curved rod from 1 to 5 microns in length and from 0 3 to 0 6 micron in thickness Morphologically the organisms vary some vibrios from a culture being small straight coccobacilli while others are curved rods the latter shapes have led to the name comma bacilli The organisms also may be double curved— S shaped and they may grow in short chains The vibrios have a single terminal flagellum and swim with a rapid darting motion which when observed under the microscope in the examination of flecks of mucus from cholera stools has led to their being likened to schools of fish swimming in a stream

The organism is gram negative and stains well with dilute (1 10) carbol fuchsin or with gentian violet It is quickly killed by drying by exposure to weak solutions of acids (0 02 to 0 05 per cent hydrochloric acid such as is common during the process of normal gastric digestion) by heating for one half hour at 55 C or by exposure to any of the chemicals usually employed for disinfection purposes Even such solutions of disinfectants as 0 5 per cent phenol will kill them in thirty minutes and 1 100 000 solutions of bichloride of mercury in ten minutes Active chlorinated lime or cyllin (solution of creolin) are said to be excellent substances for use in disinfecting cholera stools as they not only kill the cholera vibrios but also repel flies thus preventing the contamination of these insects with infected fecal material The organisms are resistant to low temperatures (they can survive in ice) may survive for several days in sea water and have been recovered from damp soil as long as five days after its contamination In sewage contaminated water the organisms are rapidly overgrown by putrefactive bacteria and soon disappear In the stools of cholera patients the vibrios usually remain alive for only a day

or two in warm weather and for about a week in cold weather They survive and multiply in fresh milk and water

When cultivated artificially the organism multiplies most luxuriously in oxygen and on alkaline media Advantage is taken of these two properties in routine bacteriologic examinations of material suspected of being contaminated (stools water etc) A satisfactory method of cultivation and identification is as follows The material to be examined is inoculated into a tube of 1 per cent peptone water (Dunham s peptone) with a pH of from 9 0 to 9 5 per cent to which is usually added 0 5 per cent sodium chloride The point *to be remembered is that* whatever the amount of suspected material added the final reaction of the peptone water culture media must be distinctly alkaline The material is then incubated for from six to twelve hours and as a result of the predilection of the vibrios for oxygen and an alkaline medium they multiply rapidly if present at the surface of the medium

At this stage examination of the surface growth by hanging drop preparation and by agglutination test may disclose the presence of *V cholerae* Ordinarily however the growth at the surface of the peptone solution is transferred (streaked) to one of the alkaline agar media Dieudonne s medium (7 parts 3 0 per cent agar 3 parts of a mixture containing equal amounts of defibrinated blood and normal sodium hydroxide) is satisfactory This highly alkaline medium stimulates growth of vibrios and retards growth of other organisms that might have carried over After incubation the resulting growth is examined by hanging drop preparations for characteristic morphology and rapidity of movement

The most important step in specific identification is the agglutination test which may be expedited by the use of the slide technique This is done in the following manner Place a drop of agglutinating serum dilution 1 200 (titer *at least 1 4000) near one end of a slide (for the test) and a drop of* saline solution near other end (for the control) With the point of an inoculating needle touch the suspected colony and rub the contents into the drop of saline Then flame the point of the needle bring it again in contact with the colony and rub the transferred material into the drop of diluted agglutinating serum If the vibrio is *V cholerae* and agglutinable evidence of agglutination will immediately be apparent in the drop containing the agglutinating serum If the slide preparations are allowed to dry and then are fixed and stained those showing agglutination reactions will usually be clearly evident in naked eye examinations A minimum of ten and preferably twenty five colonies should be tested for morphology and agglutination reaction before a negative report is rendered If during the course of the examinations vibrios are found but they fail to agglutinate subcultures should be made from the suspected colony and the resulting growth subjected to agglutination tests It has been amply demonstrated that *some strains of freshly isolated cholera* vibrios which are non agglutinable become agglutinable after they have been subcultured one or more times The reverse also is true

The Pfeiffer phenomenon was generally used for the final identification of

the *V. cholerae* until it was replaced by the now widely used agglutination test which is equally reliable and a much simpler technique

It also has been found that bacteriophages under experimental conditions affect cholera vibrios Certain bacteriophages are bacteriolytic to many strains of cholera vibrios and certain phages also produce dissociative states in strains of *V. cholerae* with resulting changes in antigenic structure

CARRIER STATE

The carrier state in cholera has been the subject of extensive investigation during the past thirty or more years Much more research needs to be done with the purpose of securing such additional reliable evidence as will put the question of the carrier state on a sounder basis

Usually *V. cholerae* (agglutinating type) can be cultured from the stools for the first three to five days of the disease It is estimated that in about 90 per cent of cases of cholera vibrios will have disappeared from the stools within ten days to two weeks A small percentage continue to excrete the organisms for from four to five weeks and occasionally the carrier state has been reported to have persisted for from five to seven weeks It is generally believed that only a very small percentage if any of individuals recovering from cholera become true chronic carriers comparable for example with the chronic carrier of typhoid organisms Though the chronic carrier state in cholera may be extremely rare available evidence indicates that temporary carriers (cases in the stage of incubation subclinical cases convalescents individuals recently recovered from cholera and healthy cholera contacts) are by far the most important source of dissemination of cholera vibrios

Irrespective of the possible influence of humidity and rainfall on outbreaks of cholera the conclusion is inescapable that the two most important factors concerned in its dissemination are the temporary carrier of cholera vibrios and mass movements of the population (religious pilgrimages and migrations of laborers engaged in seasonal occupations)

TOXINS AND PROTECTIVE ANTIBODIES

Much investigative work has been done on cholera vibrio toxins and as a result toxins of various types (endotoxins and exotoxins) have been reported There is general agreement that the most important toxin to be found in cholera vibrios is an endotoxin which is always present Filtrates of fresh cultures of cholera vibrios usually are not toxic to laboratory animals though at times they have been found to be so suggesting that exotoxins may be present The two types of toxins cannot be clearly differentiated and the general tendency at the present time is to assume that exotoxins may be present in some strains of *V. cholerae* whereas the endotoxin is present in all strains

PATHOLOGY

The blood picture in an attack of cholera is characteristic and is due to the great loss of fluid from the blood vessels and tissues of the body The red blood

cell count increases to from 7 000 000 to 8 000 000 per cmm and the proportionate increase in white cells is even greater—15 000 to 20 000 per cmm—with a relative increase in the percentage of large mononuclears and decrease in the lymphocytes The specific gravity of the blood is increased (1 060 to 1 065) and the alkalinity lowered

At postmortem examination the body shows marked rigor mortis frequently with bizarre muscular contractions there is unusual dryness of the body surface a leaden hue to the skin and marked shrivelling of the skin particularly of the hands The most striking observation when the body cavities are opened is the extreme dryness of the tissues and organs The muscles are dry and dark red in color The serous cavities are without fluid The lungs are dry and shrunken their blood vessels containing dark thick blood The right side of the heart is filled with dark viscid blood The gall bladder usually is distended with thick bile which can be forced into the duodenum only if considerable pressure is applied The obstruction to the flow of bile is caused by marked congestion of the bile duct and the adjacent duodenal mucosa and it is said that this interference with the flow of bile accounts for the rice water color of the watery evacuations The abnormalities noted in the abdomen are also striking The cavity is dry The omentum is shrivelled and dry The small intestine shows moderate congestion of the peritoneal coat and marked congestion of the mucous lining with enlargement of the lymphoid follicles The lumen of the small intestine is filled with the typical rice water material The stomach and upper part of the large intestine may show some congestion though this is not comparable in degree of severity with the congestion noted in the small intestine The kidneys (medullary portion) are markedly congested there may be minute hemorrhages between the tubules and usually there is a parenchymatous nephritis

SYMPTOMATOLOGY

During an epidemic it may be anticipated that patients will be encountered suffering with cholera of all grades of severity In the mild cases the symptoms may be those of simple diarrhea which is suspected of being cholera because of its occurrence in the course of an epidemic a tentative diagnosis that can be confirmed only by culture of cholera vibrios and positive agglutination At the other end of the scale will be the rare cases in which the patients succumb in a state of collapse before the evacuation stage is reached (cholera sicca) and in which postmortem examination shows the small intestines filled with the typical rice water material Between these two extremes will be cases exhibiting varying degrees of severity However the clinical picture exhibited by a very large proportion of the cases will conform in general to what may be designated as a typical attack of cholera

Some writers subdivide attacks of cholera into a number of clinical types *cholera sicca* *cholera gravis* the type of attack which will be discussed in some detail *cholerine* a mild type of the disease in which a stage of evacuation occurs and in which the rice water type of stool may be noted but in which

symptoms in general are so mild that there is no collapse and kidney function is not curtailed

The *incubation period* in cholera gravis ranges normally from one to five days On a basis of symptomatology a typical attack of cholera may be divided into three somewhat definite stages the stage of *evacuation* the stage of *collapse* usually designated the algid stage and finally the stage of *reaction*

Evacuation Stage In the early stage of the disease there is copious diarrhea the fluid sometimes pouring from the anus At first the stools may have a fecal tinge but they soon become watery in character containing flakes of desquamative epithelium from the mucosa of the intestines These flakes render the fresh stool more or less opaque and grayish in color and because of the characteristic color and consistency cholera stools have been likened to rice water On standing the flakes settle to the bottom The supernatant fluid is clear and may be mistaken for water The odor is albuminous The two striking features of the diarrhea are the painlessness (lack of tenesmus or colic) and more particularly the copiousness of the stools The patient not infrequently evacuates a quart or more of rice water like fluid at one time and in the course of a few hours may lose several gallons of water from the blood and body tissues

The diarrhea usually is accompanied by vomiting which at first is of the stomach contents but soon becomes rice water like in color and consistency The vomiting is distressing to the patient as the fluid sometimes gushes from the mouth At times from one to two pints of fluid may be lost in this manner contributing materially to the collapse that soon occurs as the result of the loss of such enormous amounts of fluid from the blood tissues and organs of the body The loss of fluid from the blood during an attack ranges from about one third to two thirds of the total fluid depending upon the severity of symptoms

Stage of Collapse Usually after a few hours the stage of evacuation merges into the *algid* stage The blood pressure drops markedly a systolic pressure between 60 and 75 mm Hg being common The patient is restless the face becomes shrunken and cyanotic the eyeballs are deeply sunken in the orbits the skin is cold and clammy the fingers and tissues of the hand are shrunken and wrinkled and this appearance has given rise to the expression washer woman s fingers The axillary temperature may be only 95 F or even lower at the same time that the rectal temperature is above normal and the respirations shallow and rapid There is partial or complete cessation of urinary excretion The pulse at the wrist becomes very feeble or disappears altogether Severe cramps of the muscles occur usually beginning in the toes and fingers and extending to the upper and lower extremities and even to the abdominal muscles The muscular contractions frequently produce unusual and bizarre postures The voice becomes husky and feeble the evacuations and vomiting may cease the patient becomes listless and seemingly apathetic and there is intense thirst The picture is that of shock and dehydration This algid stage may persist for a day or longer and terminates in death or the setting in of the stage of reaction

Stage of Reaction That the patient is beginning to react will become manifest when the pulse reappears the body and extremities become warm circulation is re-established the skin loses its dusky color evacuations and vomiting cease kidney function is re established with return of urinary excretion and there is in general a gradual return to normal If the stage of collapse has been very severe and has persisted for a longer period than usual the stage of reaction may be more difficult for the patient to weather than was the algid stage This is due to the fact that with the restoration of the general circulation an excessive amount of specific toxic material that has concentrated in the small intestine is absorbed in the blood vessels with consequent toxemia

The absorption of toxins during this stage may result in hyperpyrexia and continued absorption may prevent re establishment of kidney function with a resulting uremia and typhoid state With the more modern methods of treatment the stage of collapse can be minimized and the proportion of cases suffering with uremia hyperpyrexia typhoid state and other conditions of extreme gravity can be materially reduced

As was indicated in the introduction to the discussion of symptomatology the types of cholera encountered during an epidemic will be of all grades of severity although it may be anticipated that the cases seen at the beginning and through the peak of the epidemic will conform in general to the typically severe case whereas the symptomatology manifested by many of the cases arising during the late stages of the epidemic will not be so clear cut

COMPLICATIONS

Under the older methods of treatment if the stage of collapse was severe and prolonged ulceration of the cornea and sometimes gangrene of the fingers and toes and of the scrotum or the penis not infrequently developed Septic infection of the parotid gland may be a complicating condition (1 per cent of cases) and as suppuration frequently occurs incision and drainage will be required Cholecystitis is said to occur in a small percentage of cases Pneumonia of the bronchial type—small pneumonic patches difficult to detect—is a serious complication Abortion and premature delivery may be anticipated in cases of pregnancy if the attack is other than a very mild one Heart failure should be guarded against during convalescence

DIAGNOSIS

Cases of cholera encountered during the course of an epidemic can usually be diagnosed without difficulty It is the isolated or occasional atypical or mild case that is seen in areas of endemicity or epidemicity and that may prove to be the forerunner of an epidemic which presents difficulties From the viewpoint of diagnosis the most important point to be borne in mind is that *in areas of endemicity or epidemicity any case of diarrhea may possibly be cholera* This possibility should be excluded by culturing the material from the stool and examining the resulting growth for morphology and motility and by agglutination tests (page 1 0) Advantage should always be taken of

laboratory diagnostic methods to establish the diagnosis in unusual cases Their use for routine diagnosis during the course of an epidemic, though not essential is highly desirable if laboratory facilities are available

DIFFERENTIAL DIAGNOSIS

From the viewpoint of differential diagnosis the following diseases among others merit consideration

Food Poisoning If a case of suspected food poisoning is observed in an area of endemicity where cholera actually is occurring the diagnosis may be determined by laboratory examinations of the stool (morphology motility and agglutination) The symptomatology of food poisoning usually differs from that of cholera in the following respects

	Cholera	Food Poisoning
Diarrhea painful	No	Yes
Nausea	No	Yes
Abdominal pains	Rare	Constant
Tenesmus	No	Yes
Stools	Copious and resemble rice water	Liquid fecal in color offensive odor
Urine	Usually complete suppression	Never suppressed
Fever	Surface temperature below normal	Axillary temperature usually above normal

In food poisoning the attack usually involves simultaneously a number of individuals who have consumed some particular item of food

Algid Malaria Algid malaria may be mistaken for cholera but it can be quickly differentiated by the finding of the falciparum malarial parasites in blood smears and by estimating the specific gravity of the blood—in cholera the specific gravity is high due to loss of fluid elements without corresponding loss of solids and in malaria it is low due to loss of solid elements of blood (anemia)

Arsenic Poisoning The leukocytosis in arsenic poisoning is of the polymorphonuclear type whereas in cholera there is relative decrease in lymphocytes and corresponding increase in the large mononuclears

Bacillary Dysentery Fulminating attacks of bacillary dysentery may simulate cholera In bacillary dysentery there are straining tenesmus with blood mucus pus and the stools are sticky and small in amount There is also a characteristic cellular exudate in the bowel discharge Laboratory examination of the stools will make the differentiation

PROGNOSIS

The prognosis is unfavorable in old and in debilitated persons in alcoholic addicts in those with chronic nephritis and in young children Mortality rates differ widely in individual epidemics and they are also influenced materially

by the methods of treatment available Formerly the death rate ranged from 50 to 60 per cent or more and this rate still persists in outlying districts But under the system of treatment which has been developed and perfected since 1919 principally by Sir Leonard Rogers the mortality rate especially among hospitalized patients has declined to about °0 per cent

TREATMENT

The methods of treatment now generally practiced are based on the conception that therapeutic measures must be directed toward combating the profound shock from which the patient suffers as a result of toxemia with its accompanying loss of the fluid elements of the blood To compensate for the losses in fluids alkalinity and salts normal saline solutions hypertonic saline solutions and alkaline salines are administered according to the method *recently developed by Sir Leonard Rogers*

Briefly the treatment advocated by Rogers is as follows When possible treatment should be initiated before the stage of collapse thus eliminating so far as is practicable the grave symptoms incident to the algid stage However during epidemics many of the patients will be in the stage of collapse when admitted to hospital In these cases immediate intravenous administrations of saline are indicated if the extremities are cold if the pulse is poor or barely *perceptible if the patient is cyanotic and restless and if the systolic blood* pressure has dropped to 70 mm Hg or lower The specific gravity of the blood must be estimated from time to time because the amount of saline solution to be introduced is based on the specific gravity of the blood The normal specific gravity ranges from 1 056 to 1 058 If it rises to 1 062 it may be assumed that the patient has lost about 2 pints of fluid from the blood if to 1 063 about 3 pints if to 1 064 about 4 pints and if to 1 065 approximately 5 pints the *amount of saline introduced should compensate for the indicated loss*

Rogers suggests that a very simple technique for measuring specific gravity is to provide a set of eleven small bottles each bottle containing a mixture of glycerine and water of known specific gravity and being properly labeled The specific gravities should begin at 1 0,0 and increase by stages of two degrees to 1 070 The specific gravity of the patient s blood can be estimated by withdrawing a small quantity of blood in a capillary pipette and blowing it into the labeled bottles consecutively If the drop sinks in one bottle of the glycerine mixture and rises in the next consecutive bottle the correct specific gravity is between the two readings If the drop floats for a second or so before sinking the reading is the correct one

A number of instruments have been developed for measuring the specific gravity of the blood One which measures specific gravity by the falling drop method developed by Barber and Hamilton and manufactured by Eimer and Amend is being used extensively in the treatment of shock The specific gravity readings with this instrument are based on the time required for a drop of blood of known size to fall a given distance in a known period of time through a medium of known specific gravity

Rogers advocates the use of hypertonic saline solutions for the reason that the loss of salts may be greater than the loss of fluids and may actually fall below the normal of 0 85 per cent In severe cases of cholera as Sellards pointed out in 1910 acidosis is present indicating reduction in alkalinity of the blood

The temperature at which the saline should be introduced into the vein is based on the rectal temperature and therefore this should be determined before treatment is started The saline should not be warmed but should be introduced at a temperature of about 80 F which is the usual room temperature in the tropics When the rectal temperature is 101 F or higher it has been found that the administration of saline warmed to normal blood heat is apt to bring on a fatal hyperpyrexia The solutions to be injected are (1) hypertonic saline consisting of 8 gm (120 grains) sodium chloride and 0 25 gm (4 grains) calcium chloride (the calcium chloride is added because of its tonic action on the heart) dissolved in 568 cc (1 pint) of distilled or sterilized water * (2) alkaline saline solution consisting of 6 gm (90 grains) sodium chloride and 10 6 gm (160 grains) sodium bicarbonate to 568 cc (1 pint) of sterile water To prevent so far as possible the breaking down of the sodium bicarbonate it should be sterilized in a 160-grain package in an autoclave or by dry heat and should be added to the sterilized normal saline just prior to administration

Each time the treatment is administered during the stage of evacuation the patient is first given 1 pint of the alkaline saline which is followed immediately by the hypertonic saline the amount of hypertonic saline to be given being contingent on the total amount of fluid lost The intravenous injections should be given slowly as a rule about 1 pint in five minutes If during the course of the injection the patient exhibits signs of oppression (labored respiration) the rate of injection should be slowed Intravenous injections of glucose 5 or 10 per cent in normal saline are also of value as a means of combating shock

The intravenous injections should be repeated as often as may be required Blood pressure readings and specific gravity estimations should be made at least twice daily during the acute stage The saline injections should be repeated when the specific gravity of the blood rises to 1 063 or above when the patient passes large watery stools or when there is failure of the circulation as evidenced by falling blood pressure or failure of the pulse Frequently great loss in fluid of the blood results in collapse of the superficial veins In such cases it becomes necessary to incise the skin dissect around a suitable vein puncture it and insert a cannula Repeated injections can be made through the same opening in the vein if the puncture is temporarily closed by a suture lightly drawn around the vein Special flasks and cannulas with stopcocks are manufactured for use in the treatment of cholera If for any reason the intravenous route of administration of saline is impracticable the fluid should be administered intraperitoneally or under the skin Many of the mild cases of cholera do not require treatment by the intravenous route but as

* Rogers advises adding potassium chloride 0 4 gm (6 grains) to this solution

there is material loss of fluid its replacement is essential This can be accomplished by giving ½ to 1 pint of normal saline about every two hours by rectum The fluid should be run in very slowly

Recently Scudder and others have pointed out that the characteristics of the blood (physical and others) in shock and in severe cases of cholera are similar in practically all respects The importance of administering blood plasma in the treatment of shock suggests by analogy that its substitution in cholera either partially to replace or in lieu of normal and hypertonic saline might still further reduce case mortality rates

During the stage of reaction the temperature must be watched and if it rises to 103 5 F sponging with cold water is essential It is also important that the output of urine be measured and if it is less than 1 pint every twelve hours 1 pint of the alkaline saline solution (bicarbonate in normal saline) should be given intravenously and repeated as required

Two or three drugs have proved of value in the treatment of cholera Permanganate of potash in the form of pills containing 2 grains of powdered crystals of the permanganate mixed with kaolin and vaseline and coated with keratin or other type of coating is recommended Two of these pills are taken every quarter hour for the first two hours and thereafter every half hour until the stools have a greenish tinge become less copious and the stage of collapse is ended The permanganate presumably destroys the specific toxin present in the intestine and the kaolin absorbs the toxins thus preventing their entry into the general circulation Kaolin can be given in large amounts in water or as a porridge Opiates are contraindicated Rogers suggests that hypodermic injection of atropine sulphate 1/120 grain morning and evening during the stage of collapse may tend to lessen the shock

Essential oils advocated especially by Tombs are used extensively in India The mixture consists of oil of cloves oil of cajuput oil of juniper each 5 minims aromatic sulphuric acid 15 minims and spirits of ether 30 minims One drachm of this mixture in ½ ounce of water is given every half hour by mouth until vomiting and purging cease It is advised that not more than six to eight consecutive doses be given because of possible interference with kidney function

PROPHYLAXIS

General Measures

The individual and the family group can accomplish much in protecting themselves against cholera by strict attention to the hygiene of their immediate environment When cholera is prevalent in an area in which the water supply is not above suspicion it is particularly important that all water used for drinking purposes should be boiled and that in the interval between its sterilization and actual consumption it should be adequately protected against contamination If it is not practicable to boil the drinking water it may be rendered potable by the addition of a chlorine compound (chlorinated soda hypochlorite soda) or in an emergency tincture of iodine All food should

also be protected from contamination by flies or other insects Uncooked salads particularly those containing lettuce or celery are dangerous and so are raw shellfish Fruits with thick skins such as oranges bananas and avocado pears should be disinfected by immersing them in boiling water for three or four minutes or in acid solutions which are strong enough to kill the vibrios Particular effort should be made to see that the refrigerator and its contents are kept in a sanitary condition The hands should always be washed prior to eating Candy sweetmeats and foods of a similar nature should not be purchased from shops as experience has demonstrated that they attract flies and not infrequently become contaminated with cholera vibrios

Anything that tends to lower general resistance or that interferes with the normal physiologic processes will predispose people to cholera Therefore fatigue chills the use of saline purges periods of fasting the consumption of rich indigestible foods and excesses of any type should be avoided It is of the greatest importance that all stools from cases of cholera be carefully disinfected Solutions of active chlorinated lime (1 lb to 4 gals of water) or of a 5 per cent compound cresol solution mixed with the stool in equal parts are satisfactory disinfectants The disinfectant should remain in contact with the infected material for one hour Clothing and bed linen used by a patient must be sterilized by boiling or soaking in disinfecting solution Members of families nurses doctors and others coming in direct contact with cholera patients should wash the hands after exposure and remove and disinfect any clothing which may have become contaminated A practical rule is not to touch anything to be eaten for two hours after any contact with cholera as the cholera vibrios on the skin die within this period

The effectiveness of general mass control measures in areas in which cholera is epidemic will depend on the facilities and personnel available the size of the budget allotted to the project the efficiency of the organization charged with the conduct of the work and the co-operation given by the population in general General control measures should include suitable treatment of all water supplies to assure potability proper disposal of human excreta to prevent contamination of water food and insects retention of all convalescent patients in hospital or in isolation in their homes until they are free of cholera vibrios (the carrier state frequently persists for two weeks after onset of disease and occasionally for from four to six weeks or more) wholesale laboratory examinations for the detection of carriers and limitation of the movements of individuals (potential or actual carriers) within epidemic areas and to and from such areas so far as may be practical in the face of religious and social customs

Vaccination

Vaccines composed of sublethal doses of living cultures and those prepared from killed cultures of the organism produce active immunity in guinea pigs and this experimental observation has been applied to man with good results As a rule the organisms are killed by the use of 0 5 per cent carbolic acid

though formalinized vaccines have been used It is deemed highly important that the strains of *V cholerae* used in the preparation of vaccine be *freshly isolated from patients during the early stages of an epidemic* and that the strains incorporated have all the morphologic, cultural and immunologic reactions of *V cholerae* The anticholera vaccine used in India is usually prepared from a mixture of from three to six or more strains freshly isolated from individuals with cholera during the early stages of an epidemic and contains 8 000 000 000 organisms per cc

The social and religious customs in India are of such a nature that it is difficult to control the movements of the population and prophylactic vaccination to control and prevent epidemics has been resorted to on an increasingly larger scale during recent years The volume of evidence now available from India and elsewhere indicates definitely that prophylactic vaccination is of material value in preventing the disease and in curtailing epidemics

The immunity conferred by the use of vaccine is somewhat short lived usually dropping off sharply within a period of from four to six months The degree of protection afforded depends largely on the number of doses of vaccine administered Three doses should be given if feasible at intervals of between five and ten days (preferably seven day intervals) If three doses are given it is the custom in some countries to give as the first dose 0 5 cc the second 1 cc and the third 1 cc In other countries the dosage adopted is first dose 1 cc second 2 cc and third 2 cc If only one dose can be administered it should consist of 1 cc

Subsequent to the original immunization of a population group living in an area of endemicity it is highly desirable that doses of 1 cc of vaccine be given at six month intervals for the purpose of restimulating the defense mechanism of the body with consequent increases in the protective antibody content of the blood

The Japanese have recently used a heat killed vaccine sensitized by the addition of anticholera serum

Besredka and others in India have experimented somewhat extensively with anticholera vaccines administered by mouth The oral vaccine used is heat killed and is prepared with or without the addition of bile The available evidence suggests that it does protect to some extent but that subcutaneous administration (3 doses) gives better protection Comparisons of active immunity (mouse protection tests) resulting from the use of typhoid vaccine administered subcutaneously and orally have demonstrated that the subcutaneous injections give a much higher degree of protection than do vaccines administered by mouth The reactions incident to subcutaneous administration of cholera vaccines are usually so slight as to cause little or no discomfort or disability

The mouse protection test is now being used extensively in determining the virulence and protective properties of various strains of *E typhosa* and the use of this technique in the selection of strains of *E typhosa* for the preparation of typhoid vaccine has proved of material practical value It is probable that

the use of a similar technique in investigations of the virulence and protective potency of strains of V cholerae will prove to be of equal value and importance Freshly isolated strains of *E typhosa* of high protective potency and suitable for vaccine production are now being preserved for long periods of time without loss of demonstrable protective potency by a process in which they are frozen and dried at low temperature in high vacuum and then stored in sealed ampules at a low temperature The adaptation of this technique to the preservation of cultures of potent strains of *V cholerae* doubtless would be of the greatest value

Bacteriophages

During the past fifteen or more years much attention has been devoted to the investigation of bacteriophages that have relationship to cholera and the possible effects of their administration as curative and preventive agents in cholera The most important of these investigations will be those relating to the prevention of cholera If eventually it can be demonstrated that mixed phages will destroy all or even a large proportion of the strains of pathogenic cholera vibrios the wholesale administration of cholera phages to the populations in areas of endemicity or epidemicity and their implantation in drinking water supplies will constitute a far reaching and important step in the eradication of the disease These studies though promising in the nature of the results obtained have not yet reached a stage that will permit drawing any definite conclusions as to their value either in curing or preventing cholera

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SECTION TWO

DISEASES CAUSED BY BLOOD PROTOZOA

CHAPTER X

MALARIA

Z T BERCOVITZ

MALARIA IS A PARASITIC DISEASE OF THE RED BLOOD corpuscles which is caused by one of four recognized species of the genus *Plasmodium* The sporozoites of the parasite are transferred from the insect vector to the human host with the bite of the anopheline mosquito This infection is followed by prodromal symptoms and by fever chills and sweats Also blood changes occur which show a tendency to periodicity These changes are definitely related to the life cycle of the malarial parasite within the red blood corpuscle of the host

HISTORICAL NOTE

Malarial parasites were discovered by Laveran in 1880 when he observed that *Plasmodium vivax* was an intracellular pigmented body in the red blood corpuscle In 1886 Golgi recognized that these parasites were a distinct species and in 1890 Grassi and Feletti gave them a specific name

Plasmodium falciparum was also discovered by Laveran who described its crescent shaped gametocytes Golgi called attention to the fact that these gametocytes were a distinct type Working independently Marchiafava and Celli in 1889 and Canalis also in 1889 gave an accurate description of the parasite and recognized it as a new species of *Plasmodium*

Plasmodium malariae was recognized in 1881 by Laveran and once again it remained for Golgi to describe it in detail in 1886 and for Marchiafava and Celli to classify it as a separate species

Plasmodium ovale was recognized as a distinct type of *Plasmodium* by Col Charles F Craig While a military physician in 1900 he described a *Plasmodium* which he found in the blood of a soldier who was returning from the Philippines and who was suffering from tertian malaria paroxysms This parasite differed so much morphologically from *P vivax* that he came to the conclusion that it was either a distinct variety of the *P vivax* or a strain of the parasite which had been modified in form by environment Because he was uncertain of its classification he did not give the parasite a name In 19 2 the same parasite was described by Stephens who found the *P ovale* in a patient who had contracted malaria in Africa

ETIOLOGY

The etiology of malaria involves consideration of the predisposing factors and of the etiologic agents the malarial *Plasmodia*

Predisposing Factors

Although the various species of *Plasmodia* alone can give rise to malaria there are important predisposing factors that enter into the picture of the disease because of the part they play in determining the severity of the condition or the degree of immunity that can be attained

External Conditions People who show a relatively high degree of resistance to malaria frequently fall victims to the disease when they are exposed to sharp change in temperature Symptoms appear as a result of the sudden chilling of the body Because the malarial mosquito thrives in a moist climate malaria is found in damp climates rather than in dry ones Warmth also is conducive to malaria particularly in the spring and fall for at these times the mosquito is particularly active and also at these seasons the temperature changes more suddenly and sharply than in summer or winter Malaria is most frequently found in low lying areas and tends to disappear in fairly high altitudes

Otherwise healthy districts become suitable breeding places for the anopheline mosquitoes when water supplies are contaminated or when sewers are not kept in perfect condition Likewise unsuitable living conditions such as filth bad ventilation overcrowding tend to increase the number of malaria victims This is particularly true of congested areas in the tropics especially those which are surrounded by jungle and by marshy country

Systemic Conditions The general predisposing causes of malaria involve factors that lower resistance to the invading parasites and thus increase susceptibility to acute malarial attacks

Sex On the whole more men suffer from malaria than women The chief reason for this is that men are subject to greater exposure to infection

Age Children especially those who live in highly endemic areas are more susceptible to malaria than are adults The highest percentage of malarial *Plasmodia* in children is found between the first and fifth years of life Symptomatic malaria is also higher in children than in adults This difference is explained by the fact that the adult gains partial immunity as a result of repeated infections in early life

Race No race is naturally immune to malaria and there is little evidence that race plays any important part in predisposition to malarial infection It is true that native races living in endemic malarial regions suffer less from clinical malaria than newcomers to such districts Although parasites are present in the blood of the former the natives enjoy a partial immunity because of repeated attacks of malaria which increase resistance sufficiently to prevent development of the *Plasmodia* to the point of producing clinical symptoms

Heredity Immunity acquired by repeated malarial infection by the mother is not passed on to her child as children born to natives in highly endemic

areas are just as susceptible to infection as those born to parents who had not suffered from malaria The so called *family predisposition* to malaria is due to the fact that many species of malarial mosquitoes tend to linger in a house once they have gained entrance to it and to feed repeatedly on the members of the family If infected previously or if infected from any infected member of the family the mosquitoes will spread the disease through the family

Individual susceptibility to acute malaria varies greatly but apparently no one is immune to infection even though symptoms may not develop Natural resistance is weakened as a result of exposure starvation lack of a well balanced diet or other depressing conditions Newcomers into an endemic area are more likely to become infected with malaria than those who have lived there and have developed a certain degree of immunity

Malaria is not an occupational disease except in so far as their occupations may expose people to the bites of the malarial mosquitoes Toxic agents drugs fumes vapors and gases that tend to depress the system play their part in increasing susceptibility Other contributory factors include dietary deficiencies metabolic disorders exertion stress and strain mental worry and trauma Malarial infection can give rise to very serious complications in pregnancy and must be controlled as quickly as possible It is also a danger to individuals who suffer from chronic alcoholism as this condition increases susceptibility

The Etiologic Agent

The malarial parasite belongs to the genus *Plasmodium* The four species of *Plasmodium* which are recognized as responsible for the different forms of malaria are (Plates XII XIII and XIV)

Plasmodium vivax which causes vivax malaria formerly called benign tertian or simple tertian malaria

Plasmodium falciparum which causes falciparum malaria also known as malignant tertian malaria or estivo autumnal malaria

Plasmodium malariae which causes quartan malaria

Plasmodium ovale which causes ovale malaria which is a tertian type of malaria

The four species of malarial parasites belonging to the genus *Plasmodium* are pigmented and are capable of ameboid action They infect the red blood corpuscles of their host where schizogony—their asexual life—and gametogony take place Sporogony the sexual life cycle takes place within the body of the anopheline mosquito

Schizogony The purpose of schizogony is the creation of new parasites The process of schizogony begins with the attack on the red blood corpuscles by either the mature *sporozoite* injected with the bite of the mosquito or the mature *merozoite* the form developed as a result of schizogony Within the red blood corpuscle it becomes rounded and is observed to have a single nucleus It begins to absorb hemoglobin and food from the blood corpuscle and increases considerably in size The hemoglobin changes into pigment which appears in the form of dark granules within the cytoplasm of the

parasite This process continues for a period of two or three days Meanwhile the nucleus also undergoes a process of development It divides several times the number of daughter nuclei so formed depending on the species of *Plasmodium* involved The parasite then enters the schizont stage and asexual division is ready to take place The schizont divides into a series of merozoites each of which has a nucleus and cytoplasm containing pigment When the merozoite stage is reached the parasite has completely absorbed the substance of the red blood corpuscle so that when it is ready to release the merozoites into the blood stream it ruptures and with it the corpuscle ruptures also Any residuum is disposed of by phagocytes The released merozoites immediately attach themselves to other red blood corpuscles and the process of schizogony is ready to begin again

Gametogony Merozoites are capable of going through the process of schizogony again or of becoming gametocytes which is the form in which the parasite infects the mosquito Gametocytes however do not appear until schizogony has been completed several times Then some of the merozoites develop into gametocytes instead of into schizonts These gametocytes are about the same size as the schizonts but have one nucleus only and contain more pigment granules than the schizonts Male and female forms develop and these can be clearly differentiated The male forms or *microgametocytes* are characterized by an irregular diffusion of the pigment and nuclear chromatin material The females or *macrogametocytes* usually stain darker than the male The pigment is collected in a solid mass around the compact nucleus either at the center or at one side of the body Instead of undergoing schizogony these forms remain within the red blood corpuscles where they are ready to be ingested by the female anopheline mosquito If they are unable to continue their life cycle within the body of the mosquito they remain quiescent until they die

Gametocytes take about ten days to develop Usually they live for a few days although some have been known to live for as long as twenty days If the asexual cycle (schizogony) is destroyed by therapeutic measures all gametocytes disappear from the blood stream in about three weeks The periodicity of their occurrence in the peripheral circulation is directly related to the numbers of asexual forms present Fresh broods are released from the red blood corpuscles into the blood stream about ten days after schizogony is complete and they enter the blood stream daily every second day or irregularly thereafter according to their type The gametocytes of *P vivax* *P malariae* and *P ovale* are spherical in shape when fully developed while those of *P falciparum* are crescentic in shape

Sporogony The purpose of sporogony (Fig 11) is the formation of large numbers of sporozoites which cause clinical malaria when they gain entrance to the human blood stream by means of the bite of the female anopheline mosquito Sporogony takes place when the female anopheline (Fig 12) mosquito ingests gametocytes *with the blood of an individual already infected* with malaria Schizonts also ingested by the mosquito with the infected human blood do not undergo further development within the mosquito but dis

appear as digestion proceeds However the ingested gametocytes pass into the stomach of the mosquito where the blood cells containing them rupture Thus *the sexual forms escape and immediately begin to develop*

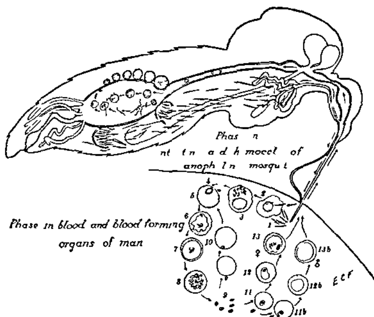


FIG 11 The life cycle of the malarial *Plasmodia* (Craig and Faust Clinical Parasitology Courtesy of Lea & Febiger)

The female forms or *macrogametocytes* become rounded as they mature and make their way toward the surface where they cause a slight bulge in the cytoplasm The male forms or *microgametocytes* develop filamentous flagella which move about continually while their nuclei break up into chromatin particles usually four to eight in number With the formation of these *flagella the male lashes its way toward the female nucleus When* fertilized the female is known as a *macrogamete* This whole process is completed rapidly As the parasite continues to develop it becomes spherical in shape and motile when it becomes a *zygote* For a time the zygote is motionless but then it undergoes a process of elongation and becomes motile a traveling vermicule or *ookinete* and as such it moves through the contents of the mosquito s stomach until it is able to attach itself to the stomach wall Forcing its way between the gut epithelium and the elastic membrane covering the stomach the ookinete comes to rest and becomes rounded with its nucleus centrally placed

The *oocyst* thus formed in the second day after ingestion is small at first but it grows rapidly while at the same time it becomes vacuolated The nucleus divides and the daughter nuclei arrange themselves along the cytoplasm between the vacuoles As nuclear division continues needle like projections of

cytoplasm pass from each nucleus into the vacuoles at either side of it By this process large numbers of filamentous structures are formed each of which contains a centrally placed nucleus These structures become the *sporo oites*

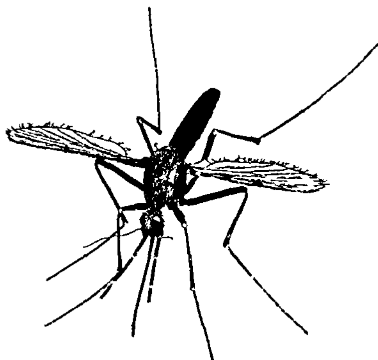


FIG 12 Model of Anopheline mosquito (Reproduced by permission of the Wellcome Research Institution)

A full developed oocyst measures from 30 to 80 microns in diameter and may contain from 1 000 to 10 000 *sporo oites* A mosquito usually has about twenty oocysts in the lining of its stomach depending on the number of gametocytes originally ingested As many as 300 to 500 oocysts have been observed If the mosquito has ingested gametocytes at one time the oocysts will mature simultaneously but if it has ingested infected blood at different times the oocysts will be at different stages of development When mature the oocyst bursts liberating sporozoites into every part of the mosquito s body particularly the salivary glands and ducts the muscles abdomen and palps These sporozoites are motile and have pointed ends and a central nucleus with an elongated nuclear membrane The mosquito is now infective and injects sporozoites with every bite

Relation of Life Cycle of Plasmodia to Malaria

There is a definite relationship between the clinical course of malaria and the developmental stages of the malarial parasite The fever chills and sweats that mark the onset of malaria occur while the parasites in the red blood corpuscles are in process of breaking up and of liberating merozoites into the blood stream The segmenting period takes place when the rigor occurs and then young parasites of the next generation can be observed as small intracorpuscular bodies (Figs 11 15 pages 139 163) In the interval between rigors when no fever is present the parasites become pigmented and may be present in large numbers Relapses in malaria when not related to fresh infection are due to the presence of a small number of resistant asexual forms which multiply when the patient s resistance is lowered

A blood film taken at the onset of a chill will reveal the presence of some nearly mature schizonts some fully developed forms and some in the actual process of rupturing and releasing merozoites Some merozoites will be seen to be within the blood corpuscles while some will be found to be adhering to the lining of the blood cell and some may have developed a vacuole and assumed the typical signet ring form A few hours after the attack only ring forms and gametocytes will be found in the blood film Twenty four hours after the chill a large number of half grown irregular schizonts and an occasional mature schizont will be found Thirty six hours after the chill the schizonts will have grown larger and there will be some nuclear matter present and possibly some division of the chromatin masses will have taken place Gametocytes in various stages of development will also be present Forty to forty five hours after the chill full grown schizonts and gametocytes will be observed in the blood film Symptoms in the patient will recur with the release of the new merozoites into the blood stream

As a rule schizogony takes place several times before the patient suffers his initial attack of malaria Thus it is usually ten or twelve days after the mosquito has injected the sporozoites before the period of incubation is over This period however varies considerably both on account of the different periods of time taken for schizogony and the fact that the resistance of some individuals to the disease is greater than that of others Symptoms from *P vivax* infection will appear in from fourteen to seventeen days from *P malariae* in from twelve to fourteen from *P falciparum* in from ten to twelve days The resistance of the individual may cause symptoms to be delayed for as long as several months

Malarial Parasites

Plasmodium vivax

P vivax (Plates XII and XIV) causes vivax malaria a form of the disease that predominates in spring and early summer

Schizogony (1) *Sporozoites* The sporozoites of *P vivax* are injected into the system with the bite of the mosquito They enter the blood stream and

PLATE XII

THE MALARIAL PARASITES

Plasmodium vivax The parasite of benign tertian malaria of man as seen in dried blood films stained with Romanowsky stain (× 2000)

1 Marginal young form

2 Arched young form

3–5 Young ring forms

6–11 Growth of schizont—enlargement of red cell formation of Schüffner's dots and development of pigment in cytoplasm of parasite

12–18 Nuclear multiplication and schizogony

19 Double infection with schizont and gametocyte

20 Double infection with two gametocytes

21–25 Growth of gametocyte

26 Female gametocyte (macrogametocyte)

27 Male gametocyte (microgametocyte)

28–29 Multiple infection with young ring forms with fused cytoplasm ("tenue phase" of Chalmers and Archibald)

30 Cell containing a nearly mature gametocyte and young form

31–35 Unusual type—absence of Schuffner's dots and little or no enlargement of red cell

(From Wenyon C M Protozoology Baillière Tindall & Cox)

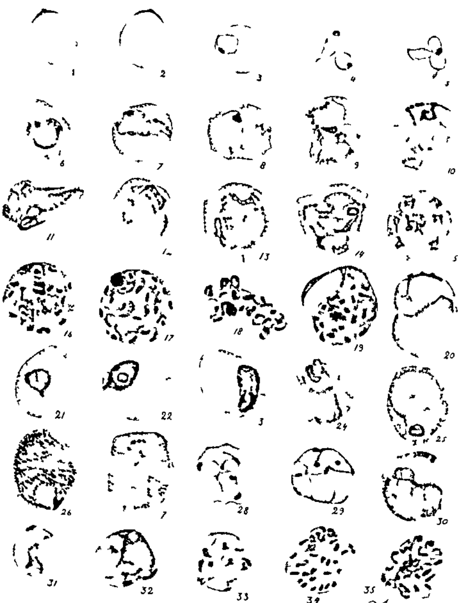


PLATE XII

PI ATL XIII

THE MALARIAL PARASITES

Plasmodium malariae and *Plasmodium falciparum* as seen in dried blood films stained with Leishman stain (X ×)

Plasmod um mal riae

1 Young ring form
Young band form
3 Slightly older parasite with granule of pigment
4–6 Growth of schizont
7–12 Nuclear multiplication and schizogony
13 Older band form of nearly mature gametocyte
14 Female gametocyte (macrogametocyte)
15 Male gametocyte (microgametocyte)

Plasmo liu n falciparum

16– 4 Young ring forms
25– 6 Growth of schizont and development of pigment these forms usually occur in the internal organs but are occasionally seen in the peripheral blood
27–30 Nuclear multiplication and schizogony these forms occur rarely in the peripheral blood
31–32 Deeply stained cells containing young ring forms and showing Stephens and Christopher s or Maurer s dots on the surface of the cell
33–35 Irregular or amoeboid young forms showing tendency to fusion of one or more parasites (*Plasm od u i tenue* of Stephens)
36–37 Developing gametocytes (crescents)
38 and 40 Female crescents (macrogametocyte) showing remains of host cell
39 Male crescent (microgametocyte)

(From Wenyon C M Protozoology Baillière Tindall & Cox)

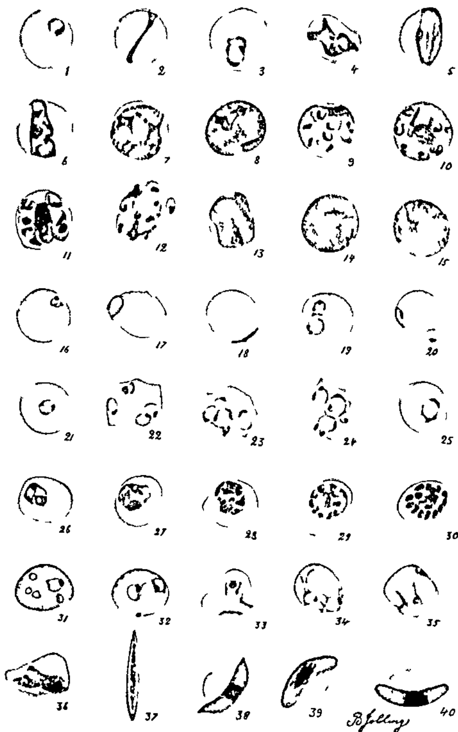

1 2 3 4 5
6 7 8 9 10
11 12 13 14 15
16 17 18 19 20
21 22 23 24 25
26 27 28 29 30
31 32 33 34 35
36 37 38 39 40

PLATE XIII

PLATE XIV

THICK AND THIN BLOOD FILMS OF MALARIAL *Plasmodia*
(Giemsa stain)

A *Plasmodium vivax*
B *Plasmodium malariae*
C Ring forms small size *Plasmodium falciparum*
D Crescents *Plasmodium falciparum*

(Redrawn from Field and Fleming, *Transactions of the Royal Society of Tropical Medicine and Hygiene* Vol XXXII Jan 1939 Vol XXXIII March 1940 and Vol XXXIV Jan 1941)

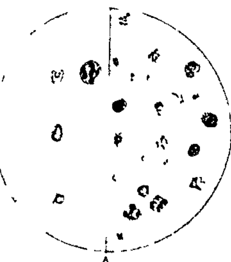








PLATE XIV

attach themselves to the red blood corpuscles At first elongated the sporozoites become rounded and assume a signet ring appearance

(2) *Merozoites* Merozoites are already in the system as they are the form of the parasite that emerges at the completion of the life cycle or schizogony within the red blood corpuscle These forms are relatively short and thick They attach themselves to the red blood corpuscles in much the same way as the sporozoites do and then they undergo the same morphologic changes as the sporozoites

(3) *Trophozoites* At this stage sporozoites and merozoites are known as trophozoites The youngest trophozoites are about 2 5 microns in diameter which is about one third the diameter of a red blood cell They consist of a more or less rounded mass of cytoplasm which stains blue with Giemsa s stain and some chromatin or nuclear material which stains pink There is usually a vacuole in the center which pushes the nuclear material to one side In five or six hours growth of the parasite begins when characteristic ameboid activity of an irregular nature can be observed The red blood corpuscle becomes pale may be enlarged to as much as 12 microns and if stained will reveal Schuffner s dots which appear as fine stippling pink in color These dots are diagnostic of infection with *P vivax* although their absence does not preclude diagnosis of *P vivax* infection in which case determination of the nature of plasmodial infection must depend on morphologic characteristics of the parasite and characteristic changes in the red blood cell

After the first five or six hours the parasite becomes either more irregular in form or else it becomes a large ring shape Its vacuole becomes larger and the cytoplasm increases gradually in size absorbing nourishment from the corpuscle Long pseudopodia are formed which connect with each other in preparation for the subsequent division of the parasite These pseudopodia give rise to greater irregularity in the shape of the parasite Pigment is either scattered throughout the cytoplasm or gathered in yellowish refractile granules within it At the same time the chromatin matter within the cytoplasm shows signs of division and when this stage is reached the parasite is known as a schizont The invaded blood corpuscle in addition to showing the Schuffner s dots will have become paler owing to the absorption of its pigment by the parasite and will also have increased in size to contain the growing schizont These changes in the corpuscle are together diagnostic of infection with *P vivax* as they are characteristic of this species and differ in nature from the changes brought about in the red blood corpuscle by other species of parasite The schizont increases in size for about thirty six hours until its cytoplasm almost fills the blood corpuscle Then nuclear division takes place and within the next twelve hours from twelve to twenty four nuclei are formed The cytoplasm also divides so that each nucleus has a body of cytoplasm The full grown schizont measures about 9 microns in diameter while each of the smaller bodies formed by processes of division measures about 1 5 microns in diameter

(4) *Merozoites* These small bodies are the merozoites which are liberated into the blood stream when the schizont bursts rupturing with it the last

vestiges of the red blood corpuscle These merozoites immediately attach themselves to fresh red blood corpuscles They then either repeat the process of schizogony or become gametocytes

Gametogony Gametocytes the sexual forms of the parasite which infects the female anopheline mosquito develop from merozoites after the process of schizogony has been completed several times They develop in the blood vessels of the bone marrow or spleen and it takes about four days for them to reach maturity When mature they are rounded in shape Although the effect of their presence on the red blood corpuscle is the same as that of the schizont they grow more slowly than the schizonts and they do not exhibit ameboid action Their pigment granules are both more numerous and more evenly distributed through the cytoplasm than are those of the schizonts and they have only a single nucleus Differentiated forms appear

(1) *Microgametocyte* or male form is about 7 to 8 microns in diameter It does not completely fill the red blood cell Schuffner s dots may be seen in the blood cell The cytoplasm which contains fine pigment granules stains a slate gray The nucleus is diffused sometimes in the form of a band of chromatin granules within the cytoplasm

(2) *Macrogametocyte* or female form larger than the male measures from 9 to 10 microns in diameter Its cytoplasm stains a deep blue with Romanowsky stains and its nucleus more compact than that of the male also stains a deeper color Its pigment is also coarser than that of the male

Sporogony The gametocytes of *P vivax* are larger than those of any other species of *Plasmodium* and it is possible that the zygotes and oocysts of *P vivax* are also correspondingly larger than those of other *Plasmodia* The pigment of *P vivax* is light brown in color while that of *P falciparum* and *P malariae* is very dark brown if not black Moreover the pigment granules of *P vivax* are frequently arranged in curved lines which serves to distinguish them from other *Plasmodia* They are fine in texture whereas those of other *Plasmodia* are coarser Thus relatively large light brown zygotes and oocysts containing fine pigment granules can be recognized as belonging to the *P vivax* species

Plasmodium falciparum

P falciparum (Plates XIII and XIV) causes falciparum malaria (estivo-autumnal or malignant tertian malaria) It is a considerably smaller parasite than *P vivax* but its life cycle is essentially the same as that of *P vivax*

Schizogony (1) *Merozoites* The merozoites of *P falciparum* are very small the smallest forms ranging from 0 5 to 0 7 micron in diameter As soon as schizogony is complete they make their way to fresh red blood corpuscles Multiple infections of red blood corpuscles occur more frequently with *P falciparum* than with other *Plasmodia* but as the parasites grow many of these cells tend to break down and disintegrate

(2) *Trophozoites* When the *P falciparum* parasite enters the red blood cell it is about one sixth the diameter of the blood corpuscle It immediately forms a vacuole and begins to grow rapidly by a process of thickening of the cytoplasm

at points contiguous to the vacuole The cytoplasm surrounding this vacuole is very narrow giving the appearance of a thin line with chromatin matter at or protruding from one side Chromatin appears either in the form of a bar or as two dots which may be close together or at opposite poles of the cytoplasm Chromatin in these forms and the minute size of the trophozoite are diagnostic of *P falciparum* Because these forms remain in the peripheral blood for at least twenty four hours they increase considerably in size and with the increase in cytoplasm the nuclear matter no longer protrudes but is buried within the cytoplasm They show relatively little ameboid activity and characteristically cause no increase in the size of the red blood corpuscle at any stage of their development

Trophozoites of *P falciparum* assume many different shapes and they frequently cause considerable confusion because of the forms they simulate Their presence can be determined however because the cells they invade change to purplish red in color when stained at this stage of development In addition malignant stippling or Maurer s dots appear and this also is characteristic of infection with *P falciparum* These dots appear as blotchy red marks and are considerably larger than the fine stippling of Schuffner s dots of *P vivax* Blood cells infected with this species of *Plasmodium* tend to adhere to each other This causes them to gather together in the blood vessels of the internal organs and in consequence the ring forms disappear from the peripheral blood after about twenty four hours With this change of location the trophozoites lose their vacuoles and become fairly compact in structure Their pigment when it appears is not diffused as it is in other species of *Plasmodia* but is collected into a mass This also serves as an important guide to diagnosis of *P falciparum* The chromatin on the other hand is scattered within the cytoplasm Nuclear division takes place when the parasite has reached its maximum size which is about two thirds the size of the red blood cell Division of the schizont will produce as many as thirty two merozoites The whole process of schizogony takes about forty eight hours Developmental forms of *P falciparum* rarely if ever appear in the peripheral circulation except just before death of the patient when occasionally they have been found

Gametogony Some merozoites of *P falciparum* like those of other *Plasmodia* develop into gametocytes which continue their life cycle in the female anopheline mosquito The youngest forms that can be differentiated from preschizont forms are rounded or oval have scattered pigment and assume a grayish tinge when stained with Romanowsky stain whereas the asexual form stains a dark blue Their chromatin matter stains more faintly and it never segments

The process of development into gametocytes takes place in the capillaries of internal organs chiefly of the spleen and the bone marrow although sometimes young forms are found in the peripheral blood Because of their characteristic shape when mature the gametocytes of *P falciparum* are called crescents

Young forms are elongated and have a slight concavity on one side and a

slight convexity on the other When deeply stained the convex side of the gametocyte can be observed to be applied to the red blood corpuscle There is some uncertainty as to whether the gametocytes develop within the red blood corpuscles or whether they are simply attached to them The young forms are considerably narrower than the mature forms although they measure about 12 microns which is about the same length as the adult gametocyte Because they are half as long again as the diameter of the red blood corpuscle they cause the blood cell to bulge at either end As they develop they become thicker until they measure from 2 to 3 microns across which is about half the diameter of the red blood corpuscle and they also become curved until they assume their characteristic crescent shape Some however do not curve but merely taper off at either end Male and female forms can be readily differentiated

(1) *Microgametocytes* or male forms have hyaline cytoplasm which stains a pink blue almost a reddish color and has fine granules of chromatin and pigment scattered through the cytoplasm

(2) *Macrogametocytes* or female forms in contrast with the microgametocytes become dark blue when Romanowsky stain is applied The cytoplasm of the female forms is denser than that of the male and instead of being scattered the nuclear chromatin and the pigment are more compact

Plasmodium malariae

P malariae (Plates XIII and XIV) the least common of the malarial *Plasmodia* in man causes quartan malaria Its life cycle is essentially the same as that of *P vivax* except for the fact that it takes seventy two hours to complete

Schizogony (1) *Merozoites* The merozoites of *P malariae* are about the same size as the equivalent forms of *P vivax* from which they are not readily differentiated They are about one third the size of a red blood corpuscle

(2) *Trophozoites* Two forms of trophozoites are found in *P malariae* the characteristic ring forms and also band forms which span the diameter of the corpuscle These band forms tend to develop at any stage of growth of the trophozoite and they are fairly common For the first twenty four hours of their development the trophozoites of *P malariae* grow slowly After six or eight hours coarse pigment begins to appear at the margin of the cytoplasm It is brown in color Unlike the *P vivax* species *P malariae* does not exhibit marked ameboid activity The pigment does not dance about as with *P vivax* but darts in and out At the end of twenty four hours the trophozoites fill about half the red blood corpuscle which however does not enlarge at any stage of the growth of the parasite At the end of the next twenty four hours the trophozoite has filled the erythrocyte and its pigment has extended from the margin of the cytoplasm until it is scattered throughout Twelve hours later the chromatin has begun to divide into masses and the pigment has begun to collect in band formation across the cytoplasm Nuclear division continues and a varying number of merozoites although usually not more than twelve form around the pigment In seventy two hours the process of schizogony is complete The merozoites so formed measure about 2 microns in diameter

Gametogony Gametocytes develop from the ring stage of the *P malariae* parasite and it takes about six days for them to reach full maturity In the earlier stages of development they are difficult to differentiate from the preschizont forms owing to the lack of ameboid activity in the latter At the end of three days gametocytes are about the same size as asexual forms at the end of two days The resemblance of the two forms is still marked but nuclear division in the asexual forms serves to differentiate them from gametocytes When fully developed the gametocytes completely fill the red blood corpuscles Their cytoplasm stains pale blue and is observed to have granules scattered throughout Chromatin matter is diffused and often assumes band forms across the cytoplasm Male and female forms develop

(1) *Microgametocytes* or male forms are slightly smaller than the macro gametocytes They stain a gray green color which is often faintly tinged with red This coloring is so characteristic that it serves to distinguish the male forms Chromatin matter is scattered throughout the cytoplasm frequently bandwise and pigment is also present

(2) *Macrogametocytes* or female forms fill the red blood corpuscles completely The cytoplasm stains a dark blue The chromatin matter is packed at one edge of the parasite while the pigment is coarser than in the microgametocyte and is plentiful

Plasmodium ovale

Because *P ovale* was regarded by some authorities as being an aberrant form of *P malariae* or *P vivax* it has been listed as a doubtful species of malarial parasite in man but it is now accepted as a distinct species It gives rise to ovale malaria which is a tertian type of malaria Its life cycle is completed in forty eight hours

Schizogony Merozoites about to undergo schizogony are about one third the size of a red blood corpuscle They bear a strong resemblance to *P malariae* at all stages of their development but unlike *P malariae* they do not develop band forms Developing trophozoites of *P ovale* are solid in structure and are not characterized by ameboid activity Band forms are found occasionally at

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Fig 13 Chief characteristics of *Culex* and *Anopheles* (Kolle and Hetsch)

Culex	*Anopheles*
1C *Eggs* laid together in small boat	1A *Eggs* separate cigar shaped *Note air floats*
2C *Larva* hangs nearly at right angles to surface of water suspended by breathing tube Feeds on particles beneath water surface	2A *Larva* lies parallel to surface of water and feeds on surface particles
3C *Body* resting position is parallel to wall and curved (angulated)	3A *Body* stands at an angle of 45 degrees and is in straight line
4C *Wings* are plain not spotted	4A *Wings* spotted
5C *Palps of the female* are shorter than proboscis	5A *Palps of the female* are the same length as the proboscis




1C




1A



2C



2A



3C



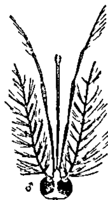
3A

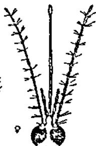


4C



4A





5C





5A

FIGURE 13

this stage of development The mature trophozoite fills the red blood corpuscle and is divided into from six to ten merozoites It has ragged edges and shows Schuffner s dots Trophozoites of *P ovale* stain a deep blue Their chromatin dots are larger than those of *P malariae* *P ovale* causes the infected and slightly enlarged blood corpuscle to become pale in color and oval in shape

Gametogony Gametocytes of *P ovale* are rounded and about the same size as the schizont forms They show no signs of segmentation These forms also resemble the gametocytes of *P malariae* but their presence in oval red blood cells which show Schuffner s dots serves to differentiate them

Exo erythrocytic Schizogony

While the process of schizogony in erythrocytes has been quite well known there has been a suspicion in the minds of malariologists that possibly some phase of development might be taking place in the other tissues This has been particularly so in discussing the question of latent infections or in dealing with the problems of recurrences without reinfection In 1931 James noted the difference in response to mosquito induced malaria and that which followed blood inoculation and suggested that sporozoites undergo special development in connective tissue or endothelium Since that time a large amount of careful work especially on bird malaria has been done and a large literature has developed Porter and Huff (1940) reviewed more than one hundred articles on the subject These authors point out that large non pigmented schizonts manifestly different from the classical schizonts found in erythrocytes have been observed in some strains of *P relictum* *P gallinaceum* *P cathemerium*, *P circumflexum* and (one unconfirmed report) *P nucleophilum* In the opinion of Porter and Huff the evidence warrants inclusion of the exo erythrocytic schizonts in the cycle of malarial parasites These authors point out that quinine does not prevent infection by sporozoites of human or avian malaria and that infection from inoculated blood however responds to these drugs

They continue That the exo erythrocytic schizonts are a part of the malarial life cycle and not a contaminant is indicated principally by the facts that they have not been separated from malaria nor shown to occur apart from it that they differ characteristically in different species of malaria and that their immunological specificity parallels that of the associated malaria Miscellaneous other evidence supports this view

After sporozoite inoculation the blood is not infective even in large quantities during the early incubation period though for most of this negative phase various internal organs and (after intramuscular inoculation) the local muscles are infective

Boyd and Kitchen (1939) showed that removal of sporozoites from the site of inoculation by infected anopheline mosquitoes did not have any effect on the course of subsequent infection In addition they demonstrated the presence of sporozoites in the connective tissue of the trabeculae in the medullary portion of an inguinal lymph node twenty four hours after inoculation with

P vivax Boyd and Kitchen make note of the fact that the sporozoites found were in the connective tissue and never in the lymphoid tissue

Kitchen (1938) demonstrated that the young forms of *P vivax* show a greater tendency to invade reticulocyte cells than mature erythrocytes This conclusion was based on a systematic and comparative study of the parasitic invasion of reticulocytes and mature erythrocytes in two patients who had moderately long spontaneously terminating *P vivax* infections Infected cells that have been described include endothelial cells and various cells of the lymphoid macrophage system (rarely granulocytes)

These studies are of the greatest importance to physicians who are concerned with tropical medicine because of their relation to the chemoprophylaxis and chemotherapy of malaria

EPIDEMIOLOGY

Malarial *Plasmodia* are found within the human system and outside the body of man they are found only in the mosquitoes that transmit them again to man Thus they are never found in water milk ice food dust soil or other fomites

Carriers

Individuals who are infected with malaria and who have gametocytes in their blood are indirectly responsible for the transmission of malaria for they infect other people Carriers as such persons are termed are responsible for the malarial infection in the localities in which they live However all individuals who have latent malarial infection are not infective to mosquitoes because all do not have gametocytes in their blood It has been demonstrated repeatedly that some individuals who are infected with the *Plasmodia* of malaria never develop gametocytes and thus never become potential sources of infection But it is safe to say that at least 50 per cent of those suffering from latent malaria develop gametocytes and so may become carriers of the infection Nevertheless not all those who have gametocytes in their blood are infective to mosquitoes for the gametocytes may not be present in sufficient numbers to transfer the infection Green (1929) found that in the case of *Anopheles maculatus* it was necessary for the peripheral blood of the infected individuals to contain at least one gametocyte of *P vivax* to 1 000 leukocytes one of *P falciparum* to 600 leukocytes and one of *P malariae* to 330 leukocytes to cause infection He and other investigators have proved that a definite relationship must exist between microgametocytes and macrogametocytes in the blood if the individual is to be infective to the mosquito

During the first days of a malarial infection gametocytes are not found in the peripheral blood they usually appear from eight to ten days after the development of symptoms In this connection it is important to remember that gametocytes may be present in the peripheral blood of many individuals who have never shown definite symptoms of infection Not only so but gametocytes are not infective to the mosquito when they first appear in the

peripheral blood they must be several days old before they become infective If they are not removed from the blood by the mosquito they do not reproduce but eventually die of old age Unless the malarial infection persists through schizogony and the consequent development of new gametocytes the infected individual becomes non infective to the mosquito

Transmission of Malaria

Cyclic and mechanical transmission constitute the two methods by which malaria infects human beings Cyclic transmission is really sporogony and involves the life cycle of the malarial parasite in its passage through the mosquito When sporogony is completed the female anopheline mosquito can transmit sporozoites with its bite Mechanical transmission of the disease can take place in several different ways

Mechanical Transmission Asexual forms can be carried by the mosquito on its proboscis from an infected individual to an uninfected person Because mosquitoes take their blood meal in the same house they can fly from one person to another and thus can transmit the malarial parasite with great rapidity

Mechanical Transmission Without Agency of Mosquito (1) *Blood transfusions* Patients upon occasion develop malaria following blood transfusion The donor may have forgotten all about his malarial symptoms but the asexual forms residual in the body are carried by the blood which is removed and when it is injected into a person with no resistance whatever development takes place After schizogony has been repeated several times sufficient parasites are developed to cause clinical malaria The length of time required for the development of malaria depends on the number of parasites given to the patient at the time of the blood transfusion and on the resistance of the new host

(2) *Contaminated syringes* Cases of malaria frequently result from the use of contaminated hypodermic syringes

(3) *Drug addicts* An ever growing problem has been created by drug addicts among whom malaria is becoming increasingly prevalent Addicts use unsterile hypodermic needles and syringes for the drug and when infected persons use them they contaminate the drug or syringe so that all subsequent users are immediately infected

Mosquitoes and Malaria

The malarial parasite is usually transmitted to the human blood stream with the bite of the female anopheline mosquito which has already been infected and in which sporogony has been completed As a rule however the mosquito conveys the sporozoites with its bite or else it conveys the asexual forms from an infected person to a non infected person as it goes from one person to another in quest of blood for its meal

The anopheline mosquito which is the malaria carrier should be clearly distinguished from the ubiquitous culex mosquito (Fig 13) The female

Anopheles has palps as long as its proboscis its wings are usually spotted and when resting its posture is almost a straight line The female *Culex* on the other hand has short palps plain unspotted wings and its head and body assume an angular position when at rest The eggs of the anopheline mosquito are cigar shaped and are supported by air floats The larvae lie horizontally beneath the surface of the water and feed on surface particles that come within their reach It is possible to destroy them without harming other organisms in the water by means of a floating insoluble poisonous dust The eggs of the culex mosquito on the contrary are in packets and are not supported by air floats The culex larvae are suspended by breathing tubes and feed on particles beneath the surface of the water In order to kill them their air supply must be shut off and this is done by pouring oil over the water in which they breed

GEOGRAPHICAL DISTRIBUTION

The geographical distribution of malaria corresponds to the distribution of the anopheline mosquitoes that act as vector Many species of anopheline mosquito are capable of transmitting malaria and in most endemic malarial areas one or more species act as transmitting agents Some other species may be experimentally infected but they are not found to be natural transmitters of malaria

Many other factors influence the transmission of malaria through the mosquito The development of the malarial *Plasmodia* in the mosquito is influenced by temperature The optimum temperature for the development of *P vivax* in most mosquitoes is 5 C The process of development usually takes about eleven days *P malariae* requires from eighteen to twenty-one days at an optimum temperature of C *P falciparum* requires a temperature of 30 C and takes from ten to eleven days Cold temperatures do not always kill the *Plasmodia* in the mosquito Humidity is also an important factor if the temperature is favorable the nearer the atmosphere is to saturation the more rapid is the development of the *Plasmodia* in the mosquito The longevity of the mosquito is important for the longer the mosquito lives the more opportunity it has to bite and so infect human beings The length of life of the mosquito is not known but sporozoites of the malarial *Plasmodia* in infected mosquitoes have been found viable and infective to man for over ninety days The percentage of infected mosquitoes is important and is often surprisingly low Although Craig found some percentages as high as 15 to 35 per cent the usual percentages vary from 1 5 to 3 per cent Other factors which are concerned are the habits of the mosquito such as the length of flight and the breeding habits for different species prefer different breeding places

IMMUNITY IN MALARIA

It has been generally accepted that malaria confers a certain degree of immunity on its host after the acute attack has subsided The mechanism associated with or responsible for this conversion of an acute attack into a chronic form the character or location of the immune response and its probable dura

tion are all questions of considerable controversy New light has been thrown on the subject by Coggeshall and his co-workers at the Rockefeller Foundation in their study of extracellular immunity in *Plasmodium knowlesi* malaria in rhesus monkeys They have demonstrated that specific protective antibodies are present in the serum of monkeys during the stage of chronic infection The concentration of these protective antibodies varies during the course of the disease as they appear to be markedly decreased immediately preceding a parasitic relapse and are present in a much higher concentration at the termination of the relapse These authors were also able to demonstrate the existence of complement fixing antibodies and agglutinating antibodies in the serum of monkeys with chronic malarial infections These findings probably represent the first direct experimental evidence of extracellular immunity in malaria and are particularly significant because of the far reaching possibilities for the better understanding of this disease From an academic standpoint their studies are of interest because they show that a host s immune responses against a pathogenic protozoan are manifested in the same way that has been demonstrated repeatedly for bacterial and virus diseases For completed papers on the study the reader is referred to the *Journal of Experimental Medicine* for the years 1937 and 1938

The immunity acquired to one species of *Plasmodium* is not effective against other species although there may be slight heterologous immunity in some instances Thus an individual who has an acquired immunity to *P vivax* is susceptible to infection with *P malariae P falciparum* and *P ovale* The immunity is not only species immunity but it is also an immunity to certain strains or varieties of the species

PATHOLOGY

Blood

Malaria is a parasitic disease of the erythrocytes As a result of infection with the *Plasmodia* the blood becomes thin and watery Not only are the red blood corpuscles to which the parasites attach themselves destroyed in the course of schizogony but many that are not attacked are also destroyed as a result of the toxins in the blood stream from the parasitic infestation Regenerative processes lead to the formation of abnormal cells of endothelial origin which replace the destroyed erythrocytes in the blood stream The surviving red blood cells show irregularities in size and shape and they usually contain less hemoglobin than healthy red blood corpuscles The total hemoglobin content of the blood may be considerably diminished as a result The hemoglobin content of the blood diminishes with each malarial paroxysm and after several of these the blood count may fall to 3 000 000 per cmm of blood Although it is doubtful whether infection with the malarial parasite can give rise to a true anemia an anemic condition is created which may persist for a considerable length of time

When schizogony is completed pigment is released into the blood stream This can be seen in the form of granules in blood smears It is rapidly absorbed

by the endothelial cells in the blood vessels and also by the mononuclear and polynuclear cells in the blood stream Thus the presence of pigmented leukocytes is of diagnostic importance

Infection with *P vivax* is characterized by enlargement of the invaded red blood corpuscles As the parasite develops within the corpuscle the blood cell becomes pale swollen and enlarged to a marked degree The degree of change in the red blood corpuscle will depend on the stage of development of the parasite at the time at which the blood smear is made At the completion of schizogony the blood cell is completely destroyed

There is no enlargement of the erythrocytes with *P falciparum* infection Ring forms and crescents only are found in blood smears of this species of *Plasmodium* because cells infected with *P falciparum* become sticky and adhere to each other as well as to the endothelial lining of the capillaries

Neither are the blood cells enlarged with *P malariae* infection Unlike *P falciparum* however all the developmental forms of this species can be found in a smear of peripheral blood In infections with *P ovale* the red blood cells are enlarged but not as greatly as in infections with *P vivax*

Leukocytes

During the initial paroxysm in malaria the number of leukocytes in the blood stream increases but soon after the onset of the disease the presence of the malarial parasite causes a reduction in the number of leukocytes and the typical leukopenia prevails If the number of large mononuclear cells which normally constitute from 1 to 3 per cent of the leukocytes present in the blood stream should increase to more than 15 per cent of the total the presence of the malarial parasite is suggestive

Spleen

Enlargement of the spleen is one of the most typical changes in the system brought about by the malarial parasite In some instances this enlargement is very pronounced particularly among native children and non immunized adults in cases of chronic malaria Microscopic examination of the spleen in such cases reveals congestion and edema of the organ as a whole When the malaria has not been treated the venous sinuses of the spleen are dilated and hemorrhages into the pulp are observed Endothelial cells in the walls of the blood vessels contain pigment infected red blood corpuscles as well as free forms of the parasite The entire spleen may be filled with parasitized red blood cells

In acute cases of malaria the spleen is dark red depending on the amount of pigment present and is soft and mushy In chronic cases it is darker some times steel gray in color and is also harder in texture

Liver

In acute malaria the liver is enlarged and varies in color from dull gray to black The appearance of the organ is characteristic in acute pernicious malaria

Radiating hepatic capillaries filled with large pigmented phagocytes (Kupffer's cells and endothelial cells) separate the columns of liver cells The Kupffer's cells may contain iron free wear and tear pigment which is not the same



FIG 14 Blockage of capillaries of brain with red blood cells infected with *P falciparum* × 910 (slightly enlarged)

as the pigment released into the blood plasma by the malarial parasite Localized hemorrhages also are found in acute malaria

Heart

Capillaries of the heart may be filled or even thrombosed with infected red blood corpuscles The heart muscle is pale and flabby and may show signs of fatty degeneration

Brain

The main pathologic feature of the brain in malaria is the blockage of the capillaries (Fig 14) with corpuscles that have been infected with *P falciparum* The brain tissue is pigmented which gives it a smoky gray color and it is often speckled with punctiform hemorrhages The pathologic findings in cerebral malaria are related to thrombosis or actual blocking of the cerebral capillaries by infected corpuscles during a massive invasion of the erythrocytes by the *P falciparum* parasites This condition has been amply demonstrated in cross sections of the arterioles and venules which showed the tendency of the infected red blood corpuscles to stick to the endothelial lining of the vessels There may be malarial granulomata which consist of a zone of necrosis or of partial necrosis surrounding one of the small blood vessels Localized hemorrhages are common and in some cases seem to be related to the zone of necrosis associated with the malarial granulomata It has been suggested by Durck (quoted by Thomson and Robertson 19 9) that the hemorrhage takes place into the tissues already weakened by the necrotic process Later the granuloma may appear as a zone of necrosed tissue surrounded by extravasated blood and having the blood vessel in the center In some cases coma seems to be referable to generalized toxemia and not of necessity associated with large numbers of parasites in the brain capillaries nor as yet with any degree of blockage of the cerebral circulation (Thomson and Robertson 1929)

Bone Marrow

The marrow of spongy bones such as the sternum and vertebrae is dark in color and congested Hemorrhages and necrotic areas may be present Because of the obstruction to the circulation of the blood pigment is deposited in the bone marrow There is also hyperplasia.

Lungs Alimentary Canal and Kidneys

Pigment may be present in these organs also and when the malaria is caused by *P falciparum* the capillaries may be clogged with infected red blood corpuscles which adhere to the walls of the blood vessels

SYMPTOMATOLOGY

Craig aptly states that the only scientific classification of the malarial fevers is that based upon the etiology of the various types of infection that is upon the species of malaria plasmodium The subject will therefore be considered under the following divisions Vivax malaria caused by *P vivax* quartan malaria caused by *P malariae* falciparum malaria caused by *P falciparum* and ovale malaria caused by *P ovale*

Prodromal Symptoms and Mode of Onset

In some patients there may be no prodromal symptoms The onset may be sudden and without warning and may consist of a chill followed by the char

Radiating hepatic capillaries filled with large pigmented phagocytes (Kupffer's cells and endothelial cells) separate the columns of liver cells The Kupffer's cells may contain iron free "wear and tear" pigment which is not the same



FIG 14 Blockage of capillaries of brain with red blood cells infected with *P falciparum* × 970 (slightly enlarged)

as the pigment released into the blood plasma by the malarial parasite Localized hemorrhages also are found in acute malaria

Heart

Capillaries of the heart may be filled or even thrombosed with infected red blood corpuscles The heart muscle is pale and flabby and may show signs of fatty degeneration

ing may increase in violence until he actually shakes the bed During this stage the pulse may be increased in frequency reduced in volume and often irregular There is intense headache and pain in the muscles of the arms and

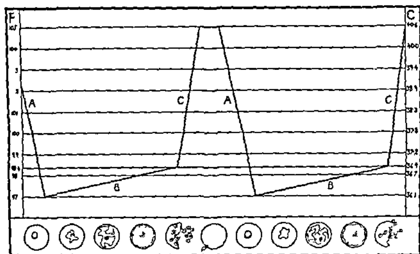


FIG 15 Chart of temperature in malaria showing relation to growth and schizogony of the parasite The temperature (*A*) falls to subnormal when the merozoites have entered the red blood corpuscles *B* gradually rises to normal as the parasite grows and *C* suddenly rises to produce fever when schizogony occurs and the merozoites and toxins are liberated into the plasma The interval *A* to *A* *B* to *B* or *C* to *C* is forty eight hours for *P vivax* seventy two hours for *P malariae* and forty-eight hours for *P falciparum* the interval *C* to *A* varies from six to twelve hours (Wenyon C M Protozoology Courtesy of Baillière Tindall and Cox)

legs the color is cyanotic and during this period the temperature rises rapidly and may reach 40 C (104 F) or more This stage may last as long as one half hour to two hours in severe cases When the patient gradually begins to feel somewhat warmer the second or hot stage begins

Hot Stage As this stage starts the patient has a combination of hot and cold sensations but soon the chilliness is lost the patient throws off all the covers and complains of intense heat He complains as bitterly of the heat as he did of the cold only a short time before His face is congested the skin of the entire body is pink to red the pulse is full and bounding often dicrotic the frequency depending on the degree of the fever Headache is usually intense nausea may be present and there may be severe pain in the muscles of the back and extremities

In mild attacks there may be no nervous symptoms but in severe infections there may be an active delirium or a drowsy condition merging into semicoma In the rare cases of pernicious malaria caused by *P vivax* coma is almost always present

The temperature may reach its highest point during this stage although

acteristic symptoms of a malarial paroxysm In most instances however for a few days before the occurrence of the actual malarial paroxysm the patients complain of prodromal symptoms such as aching bones and joints pains in the back and legs more or less malaise loss of appetite dull headache and in general they state that they feel malarial

No obviously malarial symptoms as a rule appear during the incubation period but there may be one or even two series of chills and fever before *Plasmodia* are found in the blood The actual onset of symptoms in all infections except in *P falciparum* is sudden although the patient may suffer from such conditions as headache and general malaise for an hour or so before the attack begins The malarial paroxysms usually come in the daytime although the initial paroxysm sometimes comes at night Chills last from a few minutes to a half hour or even longer The chill or rigor is succeeded by a temperature of from 40 to 40 8 C (104 or 105 4 F) The rise in temperature comes with the completion of schizogony and the liberation of the merozoites into the blood stream

In all forms of malaria the symptoms include sharp paroxysms of chills fever and sweats which recur with fairly well defined regularity according to the type of infection present If the patient is infected with *P vivax* or *P ovale* these paroxysms will recur every third day owing to the fact that in these *Plasmodia* schizogony is completed in about forty eight hours If *P malariae* is present the paroxysms will recur every fourth day because schizogony is completed in about seventy two hours *P falciparum* causes a less regular recurrence of paroxysms because there is a greater degree of irregularity in the completion of its life cycle Double infections and some falciparum infections cause frequent paroxysms at shorter intervals according to the time of release of merozoites of the different *Plasmodia* into the blood stream

Symptoms of Vivax Malaria Caused by P vivax

Vivax malaria is the most common form of the disease in temperate and tropical climates but especially in the former This type of malaria formerly called benign tertian malaria or tertian malaria is characterized by a paroxysm of chill fever and sweating occurring every forty eight hours each paroxysm being initiated by the segmentation of the *P vivax*

The malarial paroxysm when typical is divided into three stages namely the chill fever and sweating The onset of the paroxysm may occur with or without prodromal symptoms

The Chill The initial chill may be preceded or accompanied by yawning or a sense of general discomfort headache nausea and in severe infections by vomiting The feeling of cold usually starts along the spine or feet and spreads over the entire body until the patient is involved in a violent shaking chill in which the teeth chatter there are tonic and clonic muscular spasms of all the muscles of the body the patient calls for more and more covers and is completely unable to control himself in spite of hot water bottles the shak

panied by symptoms of collapse except in pernicious infections With the decline in fever the symptoms gradually disappear and the patient feels more comfortable although greatly weakened In falciparum malaria the intervals between paroxysms are very short because of the greater length of the paroxysm

The temperature curve in uncomplicated cases of falciparum malaria is characteristic At the onset the temperature rises rapidly and then there are slight oscillations covering several hours Following the period of oscillation there is a distinct fall or pseudocrisis when the temperature drops from one and one half to two degrees This in turn is followed by a secondary rise in temperature to a point as high as or higher than that attained in the initial rise The temperature curve in this infection may be divided into five distinct phases (1) the initial rise ( ) the period of oscillation or slight remission (3) the pseudocrisis (4) the precritical rise and (5) the true crisis or fall

Symptoms of Quartan Malaria Caused by P malariae

The paroxysms of quartan malaria are characterized by the regularity of their occurrence the febrile attacks coming approximately every seventy two hours corresponding to the segmentation of the *P malariae*

The clinical symptoms present during a quartan malarial paroxysm resemble so closely those observed in other malarial infections that a detailed description of them is not necessary There are the same stages of chill fever and sweating but as a rule the symptoms are more severe and pernicious attacks are more frequently fatal especially among children

Quartan malaria is much less common than the other forms of malarial infections

Symptoms of Ovale Malaria Caused by P ovale

The symptoms of infections with *P ovale* are practically the same as those of infection with *P vivax*

Relapses in Malaria

If malaria is untreated relapse is almost certain to occur Relapses are due to the fact that some forms of the parasite remain in the system after the symptoms from the initial series of paroxysms have passed away These forms are not sufficiently numerous to give rise to symptoms until the resistance of the individual has been lowered Then when conditions are favorable to their increase the parasites appear in the peripheral blood undergo schizogony and cause the symptoms which reappear as the merozoites are released in sufficient numbers into the blood stream Malaria carriers are found in areas in which malaria is endemic

Pernicious Forms of Malarial Fevers

The term pernicious malaria indicates infections in which one symptom or group of symptoms so predominates as to color the clinical picture and

at times it is highest at the end of the cold stage During the hot stage skin eruptions may appear This stage may last from four to six hours but may be either shorter or longer depending on the severity of the infection As this period draws to a close the sweating stage begins

Sweating Stage As a rule the fever begins to decline and perspiration which appears on the forehead and face rapidly involves the entire body The perspiration may be so severe that in some cases the sweat may be seen trickling over the skin on the arms and legs trunk and thighs Symptoms of collapse may appear at this time With the onset of the sweating stage the patient generally feels much better continues to improve and finally lapses into a quiet sleep that may last for several hours

Symptoms of Falciparum Malaria Caused by P falciparum

The form of malaria caused by the *P falciparum* has been variously named as *estivo autumnal subtertian or malignant tertian malaria* The *prodromal* symptoms are usually loss of appetite slight headache pains in the back and legs nervousness and general malaise In some instances the onset is so sudden that the patient has no prodromal symptoms

The paroxysm is characterized by stages of chill fever and sweating as in the other malarial infections and occurs at intervals varying from thirty six to forty eight hours coinciding with the segmentation of the *P falciparum*

The Chill The cold stage is usually initiated by yawning headache slight nausea and nervousness In most cases the distinct shaking chill that is usually observed in the infections with *P vivax* (vivax malaria) or in the quartan infections with *P malariae* is lacking in falciparum malaria Instead there are sensations of chilliness and cold along the thighs and buttocks and creeping sensations along the spine

Hot Stage This stage follows and is initiated by sensations of heat which start as localized flushings and then become generalized Then the patient has the general appearance of fever with congested eyes brilliant flushed face and hot dry skin Headache is intense and there may be great mental depression and nervous excitement Delirium or somnolence may occur at this time Pains in the back and limbs are often agonizing There may be severe pain in the abdomen Nausea and vomiting are frequently present and diarrhea may be a prominent symptom The pulse is weak rapid and may be dicrotic The temperature during this stage usually rises to 40 C (104 F) or higher although in some cases it may not go above 39 C (10° F) The hot stage may last from sixteen to twenty four hours During this time there is usually a remission when the fever falls two or more degrees The patient feels more comfortable but this remission is followed by another rise in temperature and return of the unpleasant symptoms

Sweating Stage The sweating stage follows the hot stage but it is not as well defined in falciparum malaria as in infections with *P vivax* or *P malariae* The temperature drops during this stage and there is more or less sweating but not so much as in the other types of malaria The sweating is accom

symptoms resembling those of Asiatic cholera In these cases there is severe diarrhea the stools are watery profuse blood stained or bile stained very numerous and accompanied by nausea and vomiting The diarrhea may be so great as to cause collapse the face is pinched the skin cold and clammy and there is marked cyanosis

In rare instances these patients have agonizing pain in the epigastrium or over the cardiac region and vomiting of blood stained material Hiccough is a distressing symptom and hematemesis may occur

Dysenteric symptoms may occur and are frequently associated with *P falciparum* infections The clinical picture may resemble one of the usual dysenteric diseases A certain number of these patients may have mixed infections but when a patient is in a malarial district or has been exposed to malaria blood examination for *Plasmodia* should be made

There are certain forms of pernicious malaria which simulate lobar pneumonia with cough pain in the side dyspnea and the expectoration of blood stained sputum Microscopic examination of lung sections from fatal cases has demonstrated the *Plasmodia* in large numbers in the capillaries which led to plugging rupture into the parenchyma and partial consolidation of areas sufficient to produce pneumonic symptoms

The vomiting of bile stained material associated with jaundice is a symptom which occurs especially in the pernicious forms of malaria but it may be seen in other types of infection associated with high fever

Latent Malarial Infections

Latent malarial infections are those cases in which the *Plasmodia* may be demonstrated in the peripheral blood but in which no clinical symptoms of sufficient gravity to attract attention have been noted The frequency of latent malaria varies in different localities and among different peoples

Masked Malarial Infections

Masked malarial infections include those instances in which the symptoms are obscured by some other infections or in which the symptoms so closely resemble those of some other disease as to be frequently mistaken for it The most common diseases which mask malarial infection are pulmonary tuberculosis amebic abscess of the liver articular rheumatism acute or chronic appendicitis and the dysenteries

Mixed Malarial Infections

Mixed malarial infections in which two or more of the species of malarial *Plasmodia* may occur together are not uncommon In these instances the temperature curve is usually irregularly intermittent or remittent but very often one species of *Plasmodium* so predominates that the temperature curve will be typical of that usually produced by that species and the presence of another will not be suspected until found at the time of blood examinations

threaten the life of the patient Some authorities have considered the pernicious forms of malaria as a disease entity and have confined the term to infections caused by *P falciparum* There is no species of malarial *Plasmodium* which causes only pernicious attacks although such attacks are much more common in infections with *P falciparum* than with other species of *Plasmodium*

The causes of pernicious attacks of malaria are not fully known but undoubtedly individual susceptibility to the infection pre existing disease external conditions such as locality exposure poverty and the number of *Plasmodia* of the species undoubtedly have something to do with the pernicious forms of the disease

Most cases of pernicious malaria are caused by *P falciparum* and *P falciparum quotidianum* It must not be forgotten however that *P vivax* and *P malariae* may produce pernicious symptoms

The symptoms related to the pernicious forms of malaria may be classified as comatous delirious tetanic eclamptic hemiplegic dysenteric choleraic cardialgic hemorrhagic pneumonic bilious and typhoidal

Comatous pernicious malaria is the most commonly observed form and may occur either as a sudden attack of coma or as a gradually developing comatous condition during a paroxysm of malaria Sudden development of coma is comparatively rare and unless recognized at once as of malarial origin and properly treated it is almost invariably fatal This form is very commonly seen in drug addicts The sudden onset of coma with high fever in a patient who shows evidences of frequent intravenous injections mainliners with thrombosed thickened veins along the flexor surface of the left arm (in right handed individuals) is sufficient evidence to warrant an immediate institution of an antimalarial drug usually quinine

More frequently in comatous pernicious malaria the coma develops gradually usually during the febrile stage of the paroxysm There is a tendency to somnolence which deepens into stupor and finally coma

In forms of malaria involving the nervous system the patient has hallucinations often with violent excitement or mania Symptoms may simulate meningitis with vomiting headache pain in the back of the neck convulsions and coma In some instances hemiplegia develops and in others total blindness may follow

In one of the most serious types of malaria the symptoms usually develop after one or more ordinary malarial paroxysms There is usually a condition of extreme collapse attended by profuse perspiration the temperature at the same time being more or less elevated although it may be subnormal The cheeks are drawn and pinched the eyes sunken the nostrils dilated the skin covered with perspiration and cyanotic The entire body is cold the finger nails and toe nails cyanotic. The pulse is rapid thready intermittent or irregular and the heart sounds muffled

In some instances patients with pernicious falciparum malaria may have

DIAGNOSTIC METHODS

Direct Examination of Blood

Specimens of blood for examination should be taken with great care Blood may be taken either from the finger tip or from the lobe of the ear which should be cleansed with alcohol and then pricked with a sterile needle Pressure should not be exerted the blood should be allowed to flow freely The first drops should be discarded and the drops to be used for examination should be caught with a coverslip and then placed in the center but toward one end of a grease free slide A thin film or a thick film or a method which combines both thin and thick films can be used for the purpose of distinguishing the malarial parasites

Thin Smear Method The thin film is made by placing a drop of blood at one end of a properly prepared slide The slide is then put down on a table and held firmly while another slide used as a spreader is held at an angle of about 45 degrees against the edge of the drop of blood The blood will run along the back of the spreader edge at the line of contact The spreader slide is pushed toward the other end of the slide with a smooth steady movement The blood is thus pulled or drawn behind the edge of the advancing slide The drop of blood to be spread should be so small that the film will terminate before reaching the end of the slide The film is then dried in the air and fixed with acetone free methyl alcohol before staining unless the stain used has a methyl alcohol base as is the case with Wright s stain or Leishman s stain In this case the stains are applied directly after the film is dried The methods of staining are as follows

WRIGHT'S OR LEISHMAN S STAINS

(a) Make films and air dry

(b) Cover film preparation with methyl alcohol stain for one minute (to fix)

(c) Add neutral distilled water on the slide or coverslip drop by drop until a metallic scum begins to form It is advisable to add the drops of water rapidly in order to eliminate precipitates on the blood film For all practical purposes one drop of water may be added for every drop of stain that is used

(d) Allow the mixture to remain for three or four minutes

(e) Flood with neutral distilled water to wash Do not pour off the stain but flood the slide with the distilled water thus making it impossible for precipitates to settle on the stained film The timing of the stain varies with different batches of stain when manufactured As a rule one minute of fixation and three m nutes after the water has been added is sufficient

A slight modification of this staining method has been suggested by Bercovitz as follows

The apparatus requires two staining jars with covers The reagents are pure methol alcohol and Wright s stain diluted up to 30 per cent with distilled water

One staining jar is filled with pure methyl alcohol The second contains the

Chronic Malaria

Patients who have suffered from repeated attacks of malaria and who have not had proper treatment develop a more or less severe anemia and an enlarged spleen The skin usually has a peculiar yellowish tint or an earthy pallor and the mucous membranes are pale Other symptoms include loss of appetite diarrhea dyspnea upon exertion emaciation and nervous exhaustion

Recurrent Malaria

Recurrent malaria or relapses usually occur in untreated malarial infections At the present time most malariologists accept Ross s theory regarding recurrences as the explanation of relapses in malaria and there is no doubt that short term relapses are satisfactorily explained by the continued multiplication in the human system of small numbers of the *Plasmodia* through the process of schizogony

DIAGNOSIS

The diagnosis of malaria depends on the demonstration of the malarial *Plasmodia* in the red blood corpuscles In addition to this however there are other elements which enter into the picture The leukocytes in malaria usually show a reduction in number but during the first hours of a malarial paroxysm there may be leukocytosis that is quickly followed by leukopenia The relative differential count is also changed in malaria for there is a reduction in the number of neutrophiles and an increase in the mononuclear cells especially in the large mononuclears and transitional cells Phagocytosis in malarial infections is common and examination of the blood of patients suffering from malaria always shows leukocytes containing brown or blackish pigment while some may contain *Plasmodia* and degenerated erythrocytes Smears made from the material obtained by splenic puncture show large numbers of such leukocytes The cells which act as phagocytes in malarial infections are the large mononuclear leukocytes and the reticulo endothelial cells (macrophages) of the spleen bone marrow and liver Phagocytosis appears to be most active during or directly after the chill in most malarial infections If the infection has persisted for a long time or if there is a double infection with the same *Plasmodium* or with more than one species of *Plasmodium* phagocytosis may be marked throughout the paroxysms and even between them

Melanemia is the presence of malarial pigment in the blood either free or within the leukocytes Next to the presence of *Plasmodia* melanemia is the most characteristic change that takes place in the blood in malarial infections Melanemia is seen only in malaria and its presence is therefore of great service in diagnosis if the *Plasmodia* are absent or present only in very small numbers Melanin is found in the white blood cells and tissues in the form of grains granules blocks rods irregular clumps or cylindric, polyhedra circular or irregular masses It is very dark brown and black in color

The slide should be immersed in this solution for from thirty to forty five minutes Some workers place the dried thick smear in a jar containing diluted Giemsa stain (1 drop to 1 cc) for one hour with or without previous dehemoglobinization The dehemoglobinized thick film may be fixed in acetone free methyl alcohol before staining if desired

In making parasitic surveys for malaria in endemic regions the thick film method of diagnosis is most useful Many methods of making thick films of blood have been devised but that of Barber and Kemp has proved most satisfactory The technique is as follows

(*a*) Collect large drops of blood upon carefully cleaned microscopic slides and with a needle smear the blood over an area of the slides about one half of that covered by an ordinary thin blood smear

(*b*) Allow the preparations to dry by leaving them in an incubator at a temperature of 37 C (98 6 F) for from one to one and one half hours or in a covered slide box overnight

(*c*) Dilute one part of a good Giemsa stain (this can be purchased already prepared) with six parts of neutral or slightly alkaline distilled water place the smears in this mixture and leave for about one half hour (Previous fixation and dehemoglobinization are not necessary)

(*d*) Place the smears in distilled water for about five minutes for partial decoloriza tion If the smears show a deep blue background and the leukocytes are almost black they are overstained and worthless

(*e*) Drain smears thoroughly and allow to dry They may then be examined with the 16-mm oil immersion objective

The Wright stain may be used in staining thick films but the results are not so good as with the Giemsa stain Considerable experience in the examination of such smears for the malarial *Plasmodia* is essential in order to differentiate them from other objects and this experience can be gained only through the careful examination of many such films

Combined Thin and Thick Smear The combined thin and thick smear method is valuable because with it both types of film can be studied and compared A large drop of blood is placed about one half inch from the end of the slide and is spread to a diameter of about one half inch A second drop is placed about one half inch away from the first and then the ordinary thin blood film is made After drying the thin part is fixed by standing the slide upright in a staining jar of pure methyl alcohol which should be sufficiently deep to immerse the slide to within one half inch of the thick drop After five or ten minutes for fixation it is removed from the alcohol and allowed to dry The slide kept vertical throughout this process is immersed in another vertical staining jar containing Wright s stain or Giemsa stain diluted to 1 3 with distilled water A wax glass marking pencil may be used to mark off the thick film section from the thin The drop of blood reserved for the thick film should be prepared according to the thick film technique and while this is being done care should be taken to see that the thin smear is not damaged

30 per cent solution of Wright's stain The blood film is made and dried in the usual manner It is then immersed in methyl alcohol for at least five minutes The slide is then placed in the stain for two or three minutes or more depending on the intensity of the stain desired The slide is then washed as usual

Using this technique there is no precipitation on the slide It has been found that this method is economical The stain can be used repeatedly instead of only once as in the usual technique When the fluid level of the reagents becomes low more is added until there is enough to cover the slide It is not necessary to discard any of the stain Even when the solutions are used for several months staining takes place with good results Even though the slide is in the methyl alcohol for an hour or more there is no change in the staining properties of the cells

GIEMSA STAIN

(a) The thin blood film which has been previously dried in air is placed in a staining jar in acetone free methyl alcohol for from three to five minutes

(b) Remove and allow to dry in the air Drying may be hastened by blotting between pieces of clean filter paper

(c) After fixation place the slide in another staining jar containing Giemsa stain which has been diluted using one drop of Giemsa stain to 1 cc of neutral distilled water Stain for from thirty minutes to as long as one hour if desired

(d) *Remove the slide from the stain and wash with neutral distilled water* Do not wash too long as extensive washing may tend to decolorize the stain slightly

(e) Allow to dry in the air and examine

[*Note* A convenient method of obtaining stains for use in tropical countries or in locations where it is impossible to carry large bottles of stain previously prepared is by the use of soloid microscopic stains (Burroughs Wellcome & Co) These compressed products are carefully weighed and when the directions for their use are followed exactly a very satisfactory standard preparation is available This company also prepares acetone free methyl alcohol in 10 cc ampules especially for use in making stains]

Thick Film Method The thick film is more satisfactory than the thin film when searching for parasites that occur in very small numbers in the peripheral circulation It is made by placing a large drop of blood or four or five small drops of blood on a grease free slide This blood is spread over an area of about one half inch in diameter and allowed to dry The drying must be thorough to be effective and for that reason the slide should be left in the incubator for from thirty to forty five minutes or in the open air for at least two hours Dehemoglobinization is accomplished by placing the slide in a glass of tap water until all traces of hemoglobin have gone The slide should be dried thoroughly in the air then it should be placed in a staining jar and stained Wright's stain if used should be diluted to a strength of 1 40 and should be freshly prepared each day it is to be used The slide should be left in it for from one to two hours The Giemsa stain is preferable for this type of film and 0 25 cc of this stain is added to approximately 75 cc of water

Plasmodium malariae (Quartan Plasmodium) (1) Medium size of plasmodium after development of pigment (2) No increase in the size of the infected erythrocyte (3) Absence of Schuffner s dots from cytoplasm of infected erythrocyte (4) Presence of so-called band or ribbon forms (5) Number of segments or merozoites 6 to 1 usually 8 (6) Presence of all stages of schizogony in the peripheral blood (7) Segmenting forms present in peripheral blood in 7 hours (8) Gametocytes spherical in shape

Plasmodium falciparum (Estivo autumnal or Malignant Tertian Plasmodium) (1) Small size even when fully developed filling only a part of the infected erythrocyte (2) Infected erythrocytes usually slightly smaller than normal and never enlarged (3) Presence of Maurer s dots or clefts and basophilic stippling in cytoplasm of infected erythrocyte (4) Absence of Schuffner s dots in cytoplasm of infected erythrocyte (5) Number of segments or merozoites 10 to 30 (6) Only ring forms and gametocytes usually seen in the peripheral blood (7) Gametocytes crescentic in shape

Plasmodium ovale (Ovale Tertian Plasmodium) (1) Medium size slightly larger than *Plasmodium malariae* and smaller than *Plasmodium vivax* (2) Infected erythrocyte larger than normal usually oval in shape with ragged frayed out periphery (3) Presence of Schuffner s granules even in erythrocytes containing the ring forms (4) Number of segments or merozoites 6 to 12 usually 8 (5) Presence of all stages of schizogony in peripheral blood (6) Segmenting forms present in blood in 48 hours (7) Gametocytes spherical in shape

Differentiation of Gametocytes Microgametocytes and Macrogametocytes

The differentiation of the gametocytes from the schizonts of the malarial *Plasmodia* is most important from the standpoint of the epidemiology and prevention of the malarial fevers This is possible in practically every case if attention is paid to a few simple rules of differentiation as stated by Craig as follows

The gametocytes (Plates XII XIII XIV) of *Plasmodium vivax Plasmodium malariae* and *Plasmodium ovale* may be identified by applying the following rule Any round or oval plasmodium of these species is a gametocyte if it fills the infected red blood corpuscle almost completely and if in well stained preparations it shows no division of the chromatin into distinct masses scattered throughout the cytoplasm but if on the other hand the chromatin is in a single mass or skein The gametocytes of *Plasmodium falciparum* and of the quotidian variety of this species are crescentic or kidney bean in shape

The *microgametocytes* of all species are identified by the pale blue or dark violet red staining of the cytoplasm the chromatin of the nucleus in those of *Plasmodium vivax Plasmodium malariae* and *Plasmodium ovale* is arranged in a loose pink mass or skein of fibrils or granules spindle like in shape lying in an unstained oval area that often stretches across the body of the gametocyte The microgametocytes of *Plasmodium falciparum* are not typically crescentic but have broadly rounded ends and are shaped like a kidney or lima bean

Fallacies and Puzzles in Blood Examinations

Attention has been called by Dr Andrew Balfour Director of the Wellcome Tropical Research Laboratories at Khartoum Africa to the various artefacts foreign bodies and pitfalls which are apt to confuse the laboratory worker when examining a blood film Many artefacts are due to staining or accidental contamination of a blood film with extraneous objects In addition many cells in normal blood or under various diseased conditions assume shapes suggestive of parasites and can be confused with them

Under the first group are those fallacies which come from imperfectly cleaned slides or the distilled water used for diluting the stains may have flagellates or ciliates which may be deposited on the film Yeasts fungi and other vegetable cells appear as a result of contamination from the skin or may be deposited on the slide by flies Ordinary dirt on a slide may resemble malarial pigment and flaws and cracks in the glass may take up the stain and simulate parasites of various types Hairs and bits of cotton or other fibers have been mistaken for filaria or other parasites

In the blood films made from any patient the corpuscles may be crenated vacuolated or crescent shaped In certain types of anemia the erythrocytes become changed in shape (for example sickle cell anemia) and may resemble parasites Various types of blood cells have been described under these conditions and these are shown in Plate XV Blood platelets show many variations in staining and especially when lying over a corpuscle or in it are most frequently mistaken for malarial parasites Blood platelets lying in groups often simulate crescents Leishman Donovan bodies or even trypanosomes Cabot s ring bodies Jolly bodies nucleated erythrocytes reticulocytes dividing forms of polymorphonuclear leukocytes poikilocytes vacuolated cells crenated erythrocytes and sickle cells of sickle cell anemia form the most common puzzles and fallacies in blood examinations

The Microscopic Diagnosis of the Malarial Plasmodia

The diagnosis of every malarial infection should if possible be based on the demonstration of the causative *Plasmodium* in the blood of the patient The morphology of the various species of *Plasmodia* in both unstained and stained preparations of blood has already been considered but a short summary of the differential features that can be observed in stained specimens as given by Craig in Tice s Practice of Medicine may be helpful (Plates XII XIII XIV)

Plasmodium vivax (Tertian Plasmodium) (1) Larger size especially after the development of pigment (2) Increased size of the infected erythrocyte and distortion in shape (3) Presence of Schuffner s eosinophilic granules in the cytoplasm of the infected erythrocytes (4) Number of segments or merozoites 12 to 24 (5) Presence of all stages in the life cycle in human being (schizogony) in the peripheral blood (6) Segmenting forms present in blood in 48 hours (7) Gametocytes spherical in shape



PLATE XV

PLATE XV

NORMAL AND ABNORMAL RED CORPUSCLES AND PLATELETS

(Wright's stain 1 mm = 1 micron)

FIG 1 Normal red corpuscles (normocytes)

FIG 2 Small red corpuscles (microcytes)

FIG 3 Large red corpuscles (macrocytes)

FIG 4 Exceptionally large red corpuscle (megalocyte) from a case of pernicious anemia

FIG 5 Abnormally shaped red corpuscles (poikilocytes) from cases of pernicious anemia chronic posthemorrhagic anemia and sickle cell anemia

FIG 6 Reticulocytes stained with cresyl blue as well as Wright's solution to show the granulo reticulo filamentous network

FIG 7 Red corpuscles showing polychromatophilia (diffuse basophilia)

FIG 8 Red corpuscles showing basophilic stippling (punctate basophilia) *a* *b* and *c* are from a case of pernicious anemia *d* from a case of lead poisoning The stippling in *d* is much finer than in the other cells *c* contains a large nuclear fragment *b* and *d* are diffusely basophilic

FIG 9 Red corpuscles containing Cabot's ring bodies The cytoplasm of *a* and *c* is diffusely basophilic and contains fine chromatin dust

FIG 10 Basophilic red corpuscle containing three Howell Jolly bodies a Cabot's ring body and fine chromatin dust

FIG 11 Normoblasts *e* is the youngest form the nucleus being composed of coarse strands of chromatin the nuclei of the other cells are pyknotic *c* and *d* show karyorrhexis

FIG 12 Microblasts

FIG 13 Macroblasts These differ from normoblasts chiefly in size The nuclear chromatin is quite coarse

FIG 14 Megaloblasts The nuclear chromatin is fine and there are several nucleoli in each cell The nuclear membrane is well marked The cytoplasm is markedly basophilic

FIG 15 Blood platelets *a* normal platelets *b* a giant platelet from a case of pernicious anemia *c* platelets from a case of thrombopenic purpura after splenectomy

(From Musser T H and Wintrobe M M In Tice Practice of Medicine Courtesy of W F Prior Company Inc)

Ta le I

THE DIFFERENTIAL DIAGNOSIS OF THE MALARIA PLASMODIA OF MAN (WRIGHT'S STAIN)

D tw f sch zog y	Plasmod v iv x	Plas m M la e	Pla m ium F lci a m	Pla m Ov le
M tu ty	F ty-e ght h rs	Se ty t h rs	Th ty t f ty ight h	F ty ght h rs
Pigm t (H mozo)	A u am bo d til bo t h lf grown	Slightly bo d d n g t phozo tag	A t m boid d n g t oph zo t tag	Slightly am bo d d n g troph zo t tag
I fect d red blood corpuscle	Y ll wish b w fi g d m t odl ts	D k b w lmost bl ck co rs g lumps d r gul m ll	V ry d k b w bl k g les r m ll m se	D k b wn i co rse g lea g l mass
St ges f dev l pm t see periph al blood	M h larged pal w th eosin ph l ppl g (Schüff s d ts)	N t l ged N rmal colo gra l t ppl g	N t l ged m ll rth n m t D k g re (B ssy) Baso- ph l d ts a d b k d) It yt pla m (M re l fts dots)	Som wh t l ged, al irr gul h pe w th eo ph lic stipp(l g (Schüff d t)
M lt pl fectio f ed blood pusc|	T phozo tes schizo t d g me- tocyt	T ph zo t schizo t d g m tocyt	L lly nly tr ph zo t s d g m tocytes In pe fect schizo ts m y be ly e	T ph zo tes schizo ts a d g m to- ytes
A f red blood rp scl occup d by f lly d eloped sch zo t	Qui ommo	V ry rare	V ry mm	R
T phoz tes (ri g f m)	E t ed blood rp scl h b u nl rged	Alm t t d blood rp scl which is not l ged	Fr m two-th ds t th ee-q t rs f ed blood corpuscl wh h is t nl rged	Abo t th ee-q rt rs f red blood rpuscl which is la ged
Schizo ts (t segm t g tag)	Sm ll d l n r g w th l d lly h hrom t n d t Am bo d	Sm ll d la g l gs w th vac l d ually h m ti d t	V ry m ll d l ge gs w th acuol d f eq tly th hrom t d ts P phe ll rm mm (F ppl q) Am bo d	Sm ll d l g n gs w th l Am bo d
Segm t g sch zo t	I regula bizarre f rm) prese t ea ly tage Ch m ti hn gra mall regul cl mps	O l d w th acu) ly tag Chromat coarse g n- les gula cl mps g d f rr ft see	N t ually se periph l blood Oval ro d b hrom t n l g g les d m ll l mps	R d d al with acu le ea ly t g Chrom t eg) l mps r f l me t m sses
Gametocytes	F ll gre tly nla ged ed blood pusci t 4 m rozoites (u lly 8 to) gularly r ged bo t mass f pigm t	Almost fill normal sized ed blood corpuscl 6 t m rozo tes (lly 8 t) g d) k th petals f flow nd g t l f gm nt m	N t lly see periph al blood F ll two-thi ds t th ee qu t rs f d blood rpuscl 8 (36 m o- zo t (lly 8 t 4) g d bo t t al p gm t mass	F ll bo t three-q rt rs f red blood co p scl 6 t m g d bo t t l o ec n t c p gm t mass
	R d d fill th la ged ed blood corpuscl Chromat dis- t buted yt pl m	R d d fill th normal sized red blood rp scl Ch m t n- d trib t d yt p l m	Cresce t kidney be h pe U lly pla tly f ee blood Ch t d t b t d y o- plasm	R d d fill bo t th ee-q t f th l g d r d blood p scl Ch m u d trib ted yto- plasm

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The *macrogametocytes* of all the species of malaria plasmodia are identified by the deep blue staining of the cytoplasm The chromatin of the nucleus in those of *Plasmodium vivax Plasmodium malariae* and *Plasmodium ovale* is collected in a dense red mass lying in an unstained area either at the center of or to one side of the body of the gametocyte The macrogametocytes of *Plasmodium falciparum* are more slender in shape than the *microgametocytes* and are *typical crescents with sharply rounded or pointed ends*

The most important differential features of the various species of malarial *Plasmodia* are given in Table I

DIFFERENTIAL DIAGNOSIS

The diagnosis of malaria depends on the demonstration of *malarial parasites* within the red blood corpuscles The therapeutic test with quinine that is the administration of this drug in large doses and the observation of its effect upon the temperature is completely unreliable because fevers other than malaria decline under quinine treatment It is well known that many pernicious *malarial* infections are markedly resistant to quinine administered by mouth Thus the procedure of administering quinine is not only inaccurate but dangerous because the diagnosis may be delayed so long that in pernicious infections the patient may be in grave danger or even moribund before it is made The differential diagnosis of malarial fever includes

(1) *Typhoid Fever* No other disease has been so often mistaken for malaria as typhoid fever The differential diagnosis between these two depends on the microscopic examination of the blood the blood cultures and the Widal test Very rarely there may be a combined infection with malaria and typhoid The total white blood cell count and the differential count if followed day by day in typhoid fever may be of some diagnostic value because of the presence of a relative increase in the small lymphocytes in typhoid fever Early in typhoid fever the stool cultures will be positive even before the Widal test becomes positive If all these laboratory diagnostic procedures cannot be made it may be necessary to give quinine or atabrine as in malaria in full therapeutic doses for four or five days If the condition is due to malaria alone the fever will disappear promptly

(2) *Yellow Fever* In areas where both malaria and yellow fever are endemic or epidemic differentiation is difficult without a blood examination Pernicious falciparum malaria especially with vomiting jaundice or hemorrhages is apt to be confused with yellow fever The yellowish tint of the skin the flushed face the congested eyes the severe vomiting of dark brown material resembling the dreaded black vomit high temperature and albumin in the urine furnish a clinical picture closely resembling that of yellow fever In these cases the differential diagnosis can be made only by demonstration of *Plasmodia* in the blood

(3) *Kala Azar* Kala azar is characterized by an enlarged spleen anemia and a fever which at times resembles that of certain types of malaria Microscopic examination of the blood is the only differential diagnostic method

gastro-intestinal genito urinary and glandular tracts especially the liver and the spleen Various infections of the eye and ear have been reported as sequelae of malaria

TREATMENT OF MALARIA

The treatment of malarial infections is related to the acute and chronic forms of the disease as well as to the complications At the present time three drugs are considered specific each of which has a certain value as well as limitations These drugs are quinine atabrine and plasmochin

Quinine Therapy

For a discussion of the pharmacology and toxicology of quinine the reader is referred to the various textbooks on pharmacology Quinine acts on the trophozoites schizonts and merozoites of the malarial *Plasmodia* In all probability quinine does not destroy gametocytes but acts indirectly by destroying the schizonts from which the gametocytes develop It has been proved that quinine in the concentration of the drug that is possible in the human body cannot *destroy the sporozoites of any of the species of malarial Plasmodia*

The indications for the use of quinine are in mass treatment when such therapy cannot be adequately supervised by a physician the treatment of all forms of pernicious malaria by intravenous therapy the treatment of malaria in children under five years of age and in the treatment of individuals who have a history of mental or nervous disease

Any person who comes from an endemic area of malaria to a temperate climate should be given a course of quinine 10 grains daily for eight weeks

Efficacy of Quinine In the treatment of malaria the efficacy of quinine is un doubted in the elimination of malarial infections if it is properly administered over a sufficient period of time If given for a short time only it is so ineffective that from 70 to 80 per cent of cases will relapse

Method of Administration of Quinine At the present time only two of the numerous salts of quinine are usually employed in the treatment of malaria For oral administration quinine sulphate is used for intravenous therapy the dihydrochloride Quinine should never be given by rectum or by subcutaneous injection because both methods of administration are painful inefficient and unnecessary When it is impossible to administer quinine by mouth atabrine should be used If quinine must be given by injection the intravenous route is to be preferred The absorption of quinine after intramuscular injection is slow the injections are painful and abscess formation or tissue necrosis fre quently follows

Intravenous Administration of Quinine Quinine solution to be injected is prepared as follows to 300 cc of sterile normal saline add 3 cc of a quinine dihydrochloride solution containing 1 6₅ gm (2₅ grains) of the drug and sterilize the mixture by boiling Before use it is filtered through sterile gauze heated to 48 9 C (1 o F) and placed in the intravenous solution container The apparatus for intravenous injection consists of a graduated glass receptacle

(4) *Dengue* Dengue depends on the failure to demonstrate *Plasmodia* in the blood examination and the occurrence in dengue of a skin eruption In dengue there is the typical temperature curve

(5) *Other Infections* Undulant fever puerperal fever septicemia pyelitis pyemia relapsing fevers the early stages of the eruptive fevers trypanosomiasis, Chagas s disease and tuberculosis all have to be considered in the differential diagnosis In each case the differentiation must be made upon the basis of blood smear examinations

(6) *Hepatic Abscess* Hepatic abscess caused by *Endamoeba histolytica* frequently occurs with symptoms of fever chills sweating and anemia similar to those in malaria As a rule however there may or may not have been a history *of diarrheal disease There is a leukocytosis with an increase in the neutrophilic* elements and tenderness over the liver area especially in the intercostal spaces on the midaxillary line

(7) *The Dysenteries* In some malarial infections diarrhea and dysentery are prominent symptoms Any case of diarrhea especially if blood is present calls for a careful stool examination for evidences of *E histolytica* and combined with that should be an examination of the blood for malarial *Plasmodia* because the two are not infrequently associated The possibility of bacillary dysentery with fever must also be kept in mind

(8) *Cerebral Apoplexy* Some pernicious falciparum infections simulate cerebral apoplexy Cerebral pernicious malaria is frequently manifested by a sudden attack of coma stertorous breathing loss of reflexes and other symptoms resembling apoplexy It is important to note that high fever occurs in malaria The attack of malaria is frequently found in children or young adults and the enlarged spleen and *Plasmodia* of malaria in the blood are usually associated with it In all cases of sudden loss of consciousness in a malarial area blood examinations must be made at once

(9) *Sunstroke* In tropical and subtropical regions some cases of pernicious malaria may resemble sunstroke In every instance therefore it is important in apparent cases of sunstroke to make sure that the patient is not suffering from an attack of pernicious malaria Microscopic examination of the blood is the only available means of accurate differentiation

COMPLICATIONS IN MALARIA

The most important complication to be noted is that of hemoglobinuria or blackwater fever Malaria may be complicated by almost any disease for example pneumonia typhoid fever tuberculosis organic cardiac disease albuminuria various mental and nervous conditions gastro-intestinal diseases especially amebic or bacillary enteritis typhoid fever and the eruptive fevers have been reported in the literature

Sequelae It is not always easy to differentiate sequelae from complications for many of the sequelae found are the result of complications These include primarily complications involving the nervous system the circulatory system

patients thus become carriers of malaria because they are capable of infecting mosquitoes and thus of perpetuating the infection in man

Atabrine Therapy

Atabrine is a synthetic drug introduced in 1933 for the treatment of malaria It is marketed in the United States under the name of atabrine The French have a similar drug called quinacrine which Russian chemists have produced under the name of acriquine

Atabrine which has been extensively studied has been found to be a mild gastro intestinal irritant which may even produce vomiting if given in larger doses In some individuals there is evidence that it produces cerebral irritation Large doses cause lowering of the blood pressure and changes in the vasomotor centers In therapeutic doses it may cause slight nausea and colicky pains in the abdomen In some persons the drug is deposited in the skin and causes a yellow discoloration that may last for days or weeks This does not seem to be related to liver damage it is not a jaundice but merely a deposition of the bright yellow drug in the skin Atabrine is eliminated slowly from the body It is important to bear this in mind because cumulative actions of the drug are inevitable if the doses administered are too large and if they are given over too long a period of time On the other hand it is important in the chemoprophylaxis of malaria for atabrine to remain in the circulation long enough to be of value in the prevention of acute malarial symptoms

Action of Atabrine Upon Malarial Plasmodia Atabrine is more powerful than quinine and is more effective in eliminating malarial infection It kills trophozoites schizonts and merozoites that is all the life cycle forms of all the species of malarial *Plasmodia* that develop in the human system It kills also the gametocytes of *P vivax* and *P malariae* but does not kill the gametocytes of *P falciparum* Atabrine has no destructive action upon sporozoites injected by the bite of infected anopheline mosquitoes and thus it is unable to prevent the infection of malarial parasites in the red blood cells The prompt and powerful action of atabrine upon the life cycle forms that develop from sporozoites makes it a valuable drug in the prophylaxis of malaria

Indications for the Use of Atabrine Because atabrine is more powerful than quinine it is indicated as a specific in the treatment of malaria in all adult patients It is preferred to quinine for all persons who can be kept under the personal supervision of a physician and who have no history of mental or nervous disease Atabrine is also preferable in the treatment of hemoglobinuric fever (blackwater fever) and in the treatment of any patient who has an idiosyncrasy to quinine Quinine and not atabrine should be used in the treatment of malaria in children under five years of age or for intravenous therapy in the treatment of pernicious malaria

Method of Administration of Atabrine The drug may be administered by mouth or intravenously

Dosage for administration by mouth Atabrine is furnished in tablets containing 0 1 gm (1½ grains) The adult dosage is one tablet containing 0 1 gm

open at the top connected with a rubber tube at the bottom and with a glass window stopcock and suitable needle attachment for intravenous injection The entire apparatus should be sterilized before use

Time of Administration of Quinine Quinine is best administered in divided doses at intervals of three or four hours until the total daily dosage has been administered *Quinine thus administered is much more effective than when it* is given in one large dose just before the expected paroxysm

For the elimination of a malarial infection quinine must be administered for at least eight weeks after an acute attack has subsided

Treatment of the Acute Attack in Adults Quinine sulphate in the dosage of 0 65 gm (10 grains) is administered by mouth three times daily for three or four days or until the acute symptoms have disappeared This is followed by the administration of 0 65 gm (10 grains) twice daily for three or four days and then 0 65 gm (10 grains) daily at bedtime for a period of eight weeks

Treatment of the Acute Attack in Children The following dosages of quinine are administered three times a day until the acute symptoms disappear

Less than 1 year	0 035 gm	(1/2 grain)
1 year	0 065 gm	(1 grain)
2 years	0 125 gm	(2 grains)
3 and 4 years	0 2 gm	(3 grains)
5 6 and 7 years	0 25 gm	(4 grains)
8 9 and 10 years	0 32 gm	(5 grains)
15 years and over	0 65 gm	(10 grains)

When the acute attack has subsided doses proportionate to those administered to adults should be continued daily for at least six or eight weeks

Short Term Quinine Treatment If the symptoms of the malarial attack only *are to be controlled smaller doses of quinine may be administered* For this purpose a daily dose of 1 gm (15 grains) for an adult is sufficient in most cases to stop the symptoms of the acute malarial attack if continued for from five to seven days The *Plasmodia* disappear from the blood until the next relapse This short term quinine treatment will not eliminate the infection *it con*trols the symptoms only and consequently relapses will occur Between relapses the *Plasmodia* multiply slowly and thus allow for the development of immunity This form of treatment used to be recommended in the belief that repeated relapses of malaria would produce immunity to the infection but careful studies indicate that the short term treatment with quinine has failed to do so

In addition to its ineffectiveness in developing immunity is the great danger that falciparum malarial infections may be treated with quinine on the short term principle and if such is the case pernicious symptoms that may be fatal are likely to develop during the relapses that inevitably take place Under such conditions the short term treatment with quinine would endanger the life of the patient if he is infected with *P falciparum*

Another serious objection to the method is that it favors the development of gametocytes and the subsequent transmission of malaria by the mosquito These

only one indication for the use of plasmochin and that is the presence of gametocytes of malarial *Plasmodia*

The dosage of plasmochin used is 0 01 gm (1/6 grain) twice daily for three days Some authorities have given this amount three times a day for five or six days but Craig believes that it is best to administer 0 01 gm (1/6 grain) three times a day every fourth day until the gametocytes disappear from the peripheral blood If it is impossible to control the treatment by microscopic examination of blood then it is wise to follow either the method first suggested of giving the dosage twice daily for three days or Craig s method three times a day every fourth day for from three to five such treatments

Summary of Treatment

Two drugs are effectively employed for the treatment of acute attacks of malaria and also for relapses

Quinine is given in dosage of 2 gm (30 grains) in divided doses (10 grains three times daily) for three or four days or until the acute symptoms have subsided *Following this 0 65 gm (10 grains) should be administered daily at night for at least eight weeks* If pernicious symptoms arise quinine dihydrochloride should be administered intravenously

Atabrine is used in the dosage of 0 1 gm (1½ grains) three times daily for from five to seven consecutive days If pernicious symptoms develop the atabrine should be discontinued and quinine dihydrochloride should be given intravenously If the patient is sensitive to quinine atabrine may be given intravenously Atabrine kills the gametocytes of *P vivax* or *P malariae* so that it is not necessary to administer plasmochin If the gametocytes of *P falciparum* are present plasmochin may be administered

Treatment of Malaria Infected Patients Returning from the Tropics

If quinine was taken by the patient when he left the tropics for a temperate climate its use in the accustomed dose should be continued systematically during the voyage and for two months after its conclusion The dosage to be preferred is 0 65 gm (10 grains) every evening for eight weeks

An important routine is to administer a course of therapy with atabrine for five or seven days to all who return by ship from tropical or highly endemic areas especially if they are returning during the winter months This should be followed by the administration of atabrine 0 1 gm (1½ grains) daily for two months

Treatment of Pernicious Malaria

Prompt and energetic treatment of all malarial infections showing symptoms suggestive of a pernicious character is vital for the welfare of the patient Delay in recognition and treatment of pernicious symptoms is the most common cause of death from malaria Most pernicious infections can be successfully treated if recognized promptly *Quinine should be administered intravenously immediately If for any reason quinine cannot be given atabrine should be ad*

(1½ grains) three times daily after meals for from five to seven consecutive days In relapsing cases the treatment should be continued for seven days followed by an interval of rest of two weeks and then the dosage of atabrine should be repeated For children the dosages are as follows

1 to 4 years of age	½ tablet 0 05 gm (¾ grain) twice daily for five days
4 to 8 years of age	1 tablet of 0 1 gm (1½ grains) twice daily for five days
Over 8 years of age	The same dosage as for adults

[*Note* For very young children the tablet may be crushed and suspended in syrup jam honey or some other pleasant medium]

Intravenous administration of atabrine At the present time atabrine for intravenous use is supplied in sealed ampules containing 0 2 gm (3 grains) Accompanying these are ampules containing 10 cc of sterile distilled water A solution of atabrine can be made in a sterile 10 cc syringe The solution should be crystal clear before it is given intravenously

For the treatment of pernicious malarial infection the intravenous injection of 0 1 gm (1½ grains) to 0 2 gm (3 grains) of atabrine once a day is suggested While some authorities have used larger dosages the amounts given here should not be exceeded Most of the cases in which toxic symptoms have followed the administration of atabrine have been patients to whom larger doses than those recommended have been administered or for whom treatment has been continued for more than seven days

A combination of atabrine and quinine has been suggested by Dove In this method he uses atabrine in the usual dosage for seven days followed by seven days of quinine in a total daily dose of 1 2 gm (20 grains) In the third period of therapy atabrine is given in the usual dosage for five days and *finally quinine* 1 0 gm (15 grains) daily for another five days Plasmochin may be used for a five day period at the end of the above routine to eliminate the gametocytes

Plasmochin Therapy

Plasmochin is a synthetic preparation that was brought out in 1926 under the name of Plasmoquine or Plasmoquin Originally introduced by its makers as a specific in the treatment of malaria it is no longer used for that purpose because the dosage required for the elimination of malarial infection was followed by toxic symptoms in many individuals At the present time it is employed only for the destruction of the gametocytes of the malarial *Plasmodia* following treatment with either quinine or atabrine For this purpose it can be administered in very small non toxic doses

Toxicity of Plasmochin The toxicity of plasmochin is much greater than that of either quinine or atabrine In man the mildest toxic symptoms following doses sufficient to eliminate malarial infection are cyanosis of the face lips and fingers slight jaundice dyspnea dizziness headache fever urticaria intense nervousness and epigastric and abdominal pain

Dosage of Plasmochin Plasmochin should never be used in the treatment of malaria but only for the elimination of gametocytes of the Plasmodia There is

chemoprophylaxis although no effective drug is yet available that will ensure the destruction of the sporozoites of malaria as soon as they enter the body Since atabrine first came into use in 1933 much literature has accumulated on the subject of malaria prophylaxis In many of these studies the results obtained with atabrine or quinine have been published The author has reviewed this literature and has been able to make an evaluation of the two drugs on the basis of the most valuable of these studies

Neither atabrine nor quinine will keep the blood entirely free from malarial parasites even when the drug is taken constantly in adequate dosage It has been noted however that in a large number of patients in all parts of the world the parasitic index has been definitely reduced during drug prophylaxis and that this reduction has been larger with atabrine than with quinine Definite reductions were noted also in the splenic indices under both drugs Even though there is an increase in the number of cases of malaria following drug prophylaxis chemoprophylaxis is indicated for persons going into a malarial district especially if they are going for the first time A dosage of atabrine 0 1 gm three times weekly will keep the incidence of acute malaria at the minimum The prophylactic dosage of quinine is 0 7 gm (10 grains) every night

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ministered intravenously In the treatment of blackwater fever atabrine is preferable to quinine and may be given intravenously if the symptoms are urgent.

PROPHYLAXIS

Problems connected with prophylaxis in malaria include the prevention of the disease in individuals who live in malarial regions the prevention of infection in the anopheline mosquito which is the malaria carrier and the safeguarding of individuals living in malarial regions either by ridding those areas of anopheline mosquitoes or else by rendering it virtually impossible for *mosquitoes to get within reach* of the people living in areas *infested with them*

Protection of the individual from infection with malaria means protecting him from the bite of the anopheline mosquito This can be done either by destroying the mosquito or by keeping it away from human beings Antilarval measures serve to destroy or at least to reduce the mosquito population Draining swamps destruction of breeding places as well as antilarval measures are of utmost importance in protecting people from these mosquitoes

The sanitary engineer must also see that houses in mosquito infested areas are adequately screened This involves careful screening of all openings connected with the house its basement attic or ventilators The screening itself should be of copper mesh that will not rust through easily if other kinds of mesh are used they should be kept in perfect repair Doors and windows should be screened effectively so that people inside the house will be protected when doors or windows have to be used

The use of mosquito nets for the beds is a valuable supplementary precaution to the screening of the houses The net must be of small mesh and care should be taken to see that it has no damaged or worn places It should be tucked in carefully around the mattress If punk is burned it will drive out any mosquitoes that may have found their way into the net This practice is common in the Orient In some areas where screening is impracticable large mosquito nets are hung in rooms and people spend the evenings under these huge enveloping nets Various types of punk are burned and the smoke from them aids in keeping the mosquitoes away

In addition to these mechanical precautions people who live in malarial districts should not leave their houses between sunset and sunrise The importance of this precaution was dramatically demonstrated by the experience of Carmichael Low *and his associates Their work took them to a heavily infected* malarial swamp They were most careful to be within their screened house from sunset to sunrise and as a result no one was infected with malaria But malarial mosquitoes shipped to London with their specimens infected workers there

CHEMOPROPHYLAXIS

For those who are obliged to expose themselves to mosquito bites the problem of chemoprophylaxis becomes very important Quinine and atabrine are the two best drugs we have at the present time for dealing with this problem of

healthy individuals and of patients suffering from blackwater fever are resistant to quinine Individuals who have never taken quinine have developed blackwater fever and conversely blackwater fever patients have recovered after treatment with this drug Blackwater fever appears during or soon after the malarial season

According to Manson Bahr neither plasmochin nor atabrine has proved effective in protecting individuals from blackwater fever

EPIDEMIOLOGY

Everyone who lives in an endemic area may contract blackwater fever although adult males are particularly susceptible to the disease It is generally thought that newcomers to endemic regions do not contract blackwater fever until after they have lived there for at least twelve months but cases have been reported after three or four months residence In spite of the fact that there is no such thing as racial immunity native adults apparently have an acquired immunity as a result of repeated attacks of falciparum malaria in childhood Predisposing causes include previous illnesses—especially falciparum malaria—unsuitable diet and difficulty in adjusting to new living conditions

Blackwater fever often develops after the patients have left endemic areas These persons usually have a history of attacks of malaria as a result of infection with *P falciparum*

The *geographical distribution* of blackwater fever includes the west coast of Africa and other areas in which falciparum malaria is endemic European and American men and women alike who have lived in these endemic regions have developed blackwater fever after returning home so that it is not an uncommon disease in England and other countries outside the areas of endemicity

PATHOLOGY

Pathologists are familiar with the lesions produced in the various organs of the body by blackwater fever but they are not in agreement on the subject of the mechanism of hemolysis

Blood If examined as soon as the attack of blackwater fever begins the blood will almost invariably be found to contain *P falciparum* parasites although these disappear with the destruction of the red blood corpuscles The spleen contracts suddenly when the blackwater fever begins and this contraction probably releases the hemolytic substance into the blood stream Those red blood corpuscles which escape destruction become pale Pigmented leukocytes and free pigment may be observed in the plasma The fever is followed by leukopenia and an increase in mononuclear and other leukocytes Blood urea is increased but the coagulation time and alkalinity of the blood are decreased

Liberation of hemoglobin into the blood stream can be demonstrated in the blood serum if this is examined as soon as the blackwater fever attack begins According to Manson Bahr a large proportion of the red blood corpuscles has

CHAPTER XI

BLACKWATER FEVER

Z T BERCOVITZ

BLACKWATER FEVER (HEMOGLOBINURIC FEVER MALARIAL hemoglobinuria hemorrhagic malarial fever) is an acute hemolysis that is *generally thought to be caused by Plasmodium falciparum the causative* agent in falciparum malaria The onset of blackwater fever is sudden and is accompanied by fever and hemoglobinuria This is caused by the hemolysis which liberates the hemoglobin *into the blood stream* and results in severe anemia

HISTORICAL NOTE

Deeks and James demonstrated in 1911 that *P falciparum* was invariably associated with blackwater fever Their work has been confirmed by the subsequent studies of Manson Bahr and others James inoculated patients suffering from paresis with *P falciparum* and produced hemoglobinuria

ETIOLOGY

Although authorities do not know exactly what is the etiologic factor in blackwater fever they agree that it results from repeated reinfection with *P falciparum* It is a significant fact that blackwater fever appears only in areas in which *P falciparum* is present If blood examinations are made in blackwater fever cases before too much red corpuscle disintegration has taken place the *P falciparum parasite will be found to be present Malarial pigment* which may be found at postmortem examination supplements a history of repeated malarial attacks There is also an increase in the mononuclear count Moreover blackwater fever does not appear when prophylactic measures have been adopted to prevent falciparum malaria

The theory that *blackwater fever is caused by quinine has been disproved* by the fact that patients who have been given quinine for *P vivax* infection do not develop blackwater fever whereas the disease may develop in those *with P falciparum* infection or in those living in areas of *P falciparum* endemicity Neither does quinine even when administered in large doses protect healthy individuals *In point of fact the red blood corpuscles of both*

The *onset* of blackwater fever is usually sudden and is marked by a sharp rise in temperature to 39 ½ C (103 F) or even higher The fever may then become somewhat irregular It is accompanied by muscular aches and pains especially in the lumbar region and over the liver and spleen which are en larged and can be palpated The urgent desire to pass urine results in the passage of urine that is dark almost black in color—the characteristic that gives its name to the disease The color of the urine depends on the degree of hemolysis of the red blood corpuscles and consequent hemoglobinuria Other symptoms present include epigastric pain vomiting which may be severe and diarrhea or constipation The skin becomes jaundiced a condition that may persist for some days after symptoms have subsided

The muscular pains continue and the urine becomes darker in color until the patient begins to sweat profusely As a consequence the fever subsides slowly and the urine becomes more normal in quantity and color The patient is extremely weak as a result of the attack and cardiac failure may result There may be a cessation of the fever following the initial attack or else it may return in several days with or without a recurrence of the hemoglobinuria

The symptoms are more pronounced in severe cases of blackwater fever These include much vomiting intense epigastric distress and severe liver pain The temperature may rise to 40 C (104 F) or even higher The pulse is rapid and of fair tension but as the attack continues it becomes weak and thready The urine may remain dark in color and copious or it may become scanty gummy in consistency and finally it may be suppressed altogether The decrease in the amount of urine passed in twenty four hours is an un favorable symptom Hiccough is almost invariably a fatal symptom

Most severe cases of blackwater fever terminate in death which results from sudden heart failure exhaustion or from sudden hemorrhage from the stomach or bowel One attack of blackwater fever apparently predisposes a patient to another attack usually a third attack is fatal

COMPLICATIONS

Complications of blackwater fever include partial blindness as a result of hemorrhage into the retina bronchial and lobar pneumonia pleurisy parotitis dysentery and gall stones

DIAGNOSIS

The diagnosis of blackwater fever is not difficult The symptom complex of fever blood stained urine and jaundice is diagnostic and can be readily recog nized Laboratory diagnosis involves chemical and microscopic studies of the urine and blood examinations Oxyhemoglobin is present in severe cases and methemoglobin in milder cases Hemoglobin is present in the urine also albumin granular and hyaline casts and there is an increase in urobilin *P falciparum* may be found in the blood in early stages of the disease and anemia is usually marked

been destroyed by the time the hemoglobin appears in the urine This excreted hemoglobin is the cause of the typical cylindrical plugs in the renal tubules The characteristic icterus of blackwater fever is caused by the appearance of bilirubin and methemalbumin in the blood stream Methemoglobin which is the predominating pigment in the blood serum comes from the oxyhemoglobin liberated in the course of hemolysis Hemolysis of the blood precedes the conversion of oxyhemoglobin into methemoglobin and methemalbumin

Urine In mild cases the color of the urine is yellow red or yellow brown and in severe cases it may be dark red or nearly black Albumin in varying amounts is invariably present the urine is alkaline in reaction and its specific gravity is lower than normal Spectroscopic examination shows the characteristic bands for oxyhemoglobin which appears in severe cases and for methemoglobin in less severe cases

Spleen The spleen is usually enlarged and if there is a history of repeated attacks of malaria it may show fibrosis and may be markedly pigmented It usually has much yellow pigment from the liberated hemoglobin The capillaries under microscopic examination will be observed to be congested and if observed early in the attack *P falciparum* parasites may be seen in the red blood corpuscles and also in the large endothelial cells Necrosis of the malpighian bodies is a characteristic lesion in blackwater fever

Liver The size and color of the liver as of the spleen depend on the previous malarial history Liver cells when examined under the microscope are observed to have a cloudy swelling to contain much yellow pigment and to have under some conditions areas of necrosis The capillaries are congested and may contain pigment as a result of malaria

Kidneys The kidneys show marked congestion in blackwater fever a condition which is shown to be severe by the blood which pours from the surface when this is cut They are enlarged and their color is intensified in more severe cases The capillaries and malpighian tufts are congested the latter may be necrotic When the patient does not die for some weeks following an attack of blackwater fever the kidneys have the appearance of subacute parenchymatous nephritis whereas when death takes place early in the disease the kidneys have the appearance of acute tubular nephritis

SYMPTOMATOLOGY

There is no true period of incubation in blackwater fever although there may be what has been called a pre blackwater stage This may last for a considerable time and is found in patients who have had several slight attacks of falciparum malaria Manson Bahr points out that patients with high fever and large numbers of *P falciparum* in the peripheral blood seldom develop blackwater fever Symptoms of the pre blackwater stage include persistent headaches slight irregular fever sallow complexion icteric conjunctivae enlarged tender and congested liver and enlarged spleen Constipation is present and the urine is dark and contains some albumin

It is highly undesirable for patients who have recovered from one attack to remain in localities in which malaria and blackwater fever are endemic

TREATMENT

The treatment of blackwater fever demands skill and careful nursing During the pre blackwater stage the patient should be made to rest in bed as soon as his temperature rises the skin should be kept warm and full protection from drafts should be assured Solid food should not be taken but the patient should be encouraged to drink large quantities of alkaline drinks that are heated to room temperature He should take these in small amounts at a time If hemoglobinuria develops the patient should not be moved and should not be allowed to sit up in bed in order that danger from cardiac failure may be avoided He should not be allowed to get up until his temperature has returned to normal and has remained so for at least two days

If malarial *Plasmodia* are present the patient should be given atabrine in doses of 1½ grains (0 1 gm) three times a day for from five to seven days Atabrine is safer than quinine for the latter involves a much greater risk of precipitating an attack of hemoglobinuria in susceptible individuals than the former The blood should be examined daily beginning about five days after the cessation of hemoglobinuria and continued for at least two weeks If *Plasmodia* are found a course of atabrine should be given to prevent a recurrence of symptoms

A mild saline cathartic may be given at the beginning of an attack of blackwater fever but no subsequent cathartics should be given If vomiting should prove intractable a 5 per cent solution of glucose in normal saline should be given a pint at a time by intravenous injection The rate of infusion by intravenous injection should not be more rapid than 30 to 40 drops per minute At this rate large amounts of the glucose solution can be given in the twenty four hours In very weak patients as much as 2 500 or 3 000 cc can be administered in twenty four hours Whenever intravenous injections are given it is important to watch the circulation carefully to guard against cardiac failure The glucose solution may also be administered by rectal instillation by the drip method

Blood Transfusions Blood transfusions are important in modern methods of treatment of blackwater fever The blood may be given as citrated whole blood in amounts of 500 cc every twenty four hours or even twice in the twenty four hours if the condition of the patient is particularly serious Great care must be exercised in the typing and cross matching of the blood because the cells in severe hemolytic cases are prone to auto-agglutination While the transfusion is being given the patient must be carefully watched If any marked adverse reaction takes place the immediate injection of 0 6 cc (10 minims) of epinephrin should prove efficacious

Plasma Therapy When it is impossible to have the careful cross matching and typing that is essential for blackwater fever patients blood plasma should be used Its great value lies in the fact that cross matching and typing are un

DIFFERENTIAL DIAGNOSIS

Differential diagnosis involves hematuria paroxysmal hemoglobinuria quinine hemoglobinuria yellow fever and Weil s disease all of which are characterized by symptoms that may possibly be confused with those of blackwater fever

Hematuria which is frequently confused with blackwater fever can be readily differentiated if the clinical symptoms present are carefully observed and if a microscopic examination is made of the urine The absence of hemoglobinuria and of the acute symptoms of blackwater fever is a clinical indication of hematuria whereas the presence of numerous red blood corpuscles in the urine which can be observed by microscopic examination indicates the presence of hematuria

Paroxysmal hemoglobinuria is very rare and it usually follows earlier attacks of hemoglobinuria which occur in patients who have never been in malarial areas and have had no possible contact with either malaria or blackwater fever The clinical symptoms are less severe than in blackwater fever Yorke s autolytic reaction is thought by some authorities to be of some value in differential diagnosis

Quinine hemoglobinuria is also very rare and is found in patients who have an idiosyncrasy to quinine As soon as quinine is administered to these patients the symptoms of hemoglobinuria appear However the other symptoms of blackwater fever are absent and the hemoglobinuria disappears when the quinine is discontinued Other drugs used in the treatment of malaria such as salvarsan plasmochin and atabrine have on rare occasions given rise to hemoglobinuria

Falciparum malarial infections in which vomiting diarrhea jaundice fever and dark colored urine are the chief symptoms may be distinguished from blackwater fever by the absence of hemoglobinuria and by the promptness with which the symptoms disappear when treated with quinine

Yellow Fever may be distinguished from blackwater fever by the distinctive lack of correlation between the pulse and temperature in yellow fever and also by the fact that hemoglobinuria is not a symptom of yellow fever

Weil s Disease is a spirochetal infection which can be distinguished from blackwater fever by the absence of hemoglobinuria the presence of hematuria the marked jaundice which appears in two or three days following onset of the disease and the neutrophilic leukocytosis

PROGNOSIS

The prognosis of blackwater fever is almost invariably grave so that every case should be taken seriously Some cases however are so slight that the symptoms pass almost unrecognized but the usual case presents the classical symptom complex and the prognosis is grave and uncertain Severe chills excessive vomiting hiccough anuria and recurrence of hemoglobinuria are unfavorable symptoms The average mortality rate is from 25 to 30 per cent

AFRICAN TRYPANOSOMIASIS

E. R. KELLERSBERGER AND Z. T. BERCOVITZ

TRYPANOSOMIASIS (AFRICAN SLEEPING SICKNESS) IS A SPEcific disease that appears when the vascular system and tissues of man are invaded by elongated flagellated protozoa known as trypanosomes. In Africa the disease is caused by *Trypanosoma gambiense* and *Trypanosoma rhodesiense*; in South America by *Trypanosoma cruzi*. African trypanosomiasis is characterized by inflammatory changes in the lymphatic system and meningoencephalitis. These changes are accompanied by symptoms which include chronic irregular fever, emaciation, skin eruptions, local edema, weakness, adenitis, tachycardia, physical and mental lethargy—the so-called sleeping sickness—and which in most instances terminate in the death of the patient. The natural evolution of the disease is toward a fatal termination.

HISTORICAL NOTE

Gruby (1843) gave the generic name of *Trypanosoma* to a flagellate, *Trypanosoma sanguinis*, which had been found in the blood of frogs. Gros (1845) found this flagellate in the blood of moles and mice, and Chausset (1850) found it in the blood of rats. In the blood of a patient in West Africa Ford (1902) found motile organisms that Dutton identified as trypanosomes and called *Trypanosoma gambiense*. Castellani (1903) found the same organism in the cerebrospinal fluid of patients suffering from sleeping sickness. Thus the relationship between sleeping sickness and trypanosomiasis was found, and it was later definitely established by Bruce and Nabarro, who found the trypanosomes either in the blood, the lymphatic glands, or the cerebrospinal fluid of almost all the patients with sleeping sickness whom they examined.

Bruce (1895) isolated a trypanosome while investigating fly-borne diseases in domestic animals in Zululand, and he was able to prove that the trypanosome was transmitted by the bite of the tsetse fly. Kleine (1909), who found that the *T. gambiense* underwent a cyclic development in the tsetse fly, also discovered that infected flies retained their infection for some time. Fantham and Stephens (1910) found trypanosomes in the blood of a patient in Rhodesia, but when they examined the parasite they found that in some short forms the nucleus was in a posterior position.

necessary Plasma is a particularly valuable agent in combating shock and in supporting the patient and transfusions of 500 cc of plasma twice daily are often instrumental in saving life

Alkali Therapy Alkalies should be given in large amounts until the urine is distinctly alkaline in order to prevent plugging of the renal tubules and anuria resulting from hemolytic reaction of blackwater fever To this end sodium bicarbonate may be used either alone or with massive doses of sodium citrate Four grams of sodium bicarbonate may be given every four hours until the urine is strongly alkaline If the symptoms are very severe it may be desirable to give intravenous injections of sodium bicarbonate in quantities of 10 gm to 1 pint of distilled water This solution should be administered very slowly

Antipyretic drugs should be avoided and if the fever is unduly high the patient should be sponged with tepid water Cardiac symptoms should be treated in the usual way as they arise Hot fomentations may be applied to relieve the distress caused by scanty urine or by suppression of urine Food should be withheld during the paroxysm but milk should be given if the patient can retain it

Fluids should be given in every possible manner by mouth by infusion and by clysis For fluids by mouth fruit juices are of great value A good mixture is made by adding 1 gm (15 grains) of sodium bicarbonate or citrate to each pint of fruit juice Weak tea supplies the patient with fluid and sugar and it also stimulates the kidneys Infusion of fluids by intravenous injection is the best means of getting fluids into the system Glucose and alkalies are administered in this way

PROPHYLAXIS

Prophylactic measures that are of value in malaria are also suitable for blackwater fever Care should be taken to avoid chills overexertion and anything that reduces resistance to disease Alcoholic stimulants should not be taken and atabrine should be used instead of quinine for prophylaxis as well as for treatment If possible the individual should move away from localities in which malaria and blackwater fever are endemic

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CHAPTER XII

AFRICAN TRYPANOSOMIASIS

E R KELLERSBERGER AND Z T BERCOVITZ

TRYPANOSOMIASIS (AFRICAN SLEEPING SICKNESS) IS A SPEcific disease that appears when the vascular system and tissues of man are invaded by elongated flagellated protozoa known as trypanosomes In Africa the disease is caused by *Trypanosoma gambiense* and *Trypanosoma rhodesiense* in South America by *Trypanosoma cruzi* African trypanosomiasis is characterized by inflammatory changes in the lymphatic system and meningoencephalitis *These changes are accompanied by symptoms which include* chronic irregular fever emaciation skin eruptions local edema weakness adenitis tachycardia physical and mental lethargy—the so-called sleeping sickness—and which in most instances terminate in the death of the patient The natural evolution of the disease is toward a fatal termination

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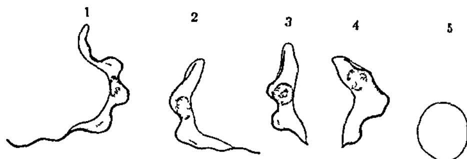


Fig 16 *Trypanosoma gambiense* 1 Long narrow form 2 intermediate form 3 thick stumpy form 4 posterior nuclear form 5 red blood corpuscle (Blacklock and Southwell A Guide to Human Parasitology Courtesy of William Wood & Company)

1 2 3 3 4 4

Fig 17 1 *Leishmania* 2 *Leptomonas* 3 *Crithidia* 4 *Trypanosoma* (Blacklock and Southwell A Guide to Human Parasitology Courtesy of William Wood & Company)

ETIOLOGY

Trypanosomes are elongated flagellates (Fig 16) that vary in size from 18 to 39 microns in length and from 1 5 to 4 microns in breadth They have rounded or oval nuclei which are usually relatively large and take the Leish

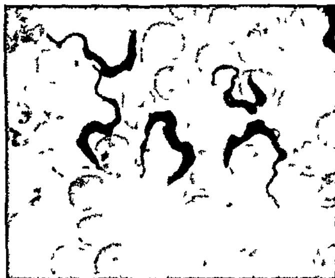


Fig 18 *Tryp osoma mbiense* (Courtesy of U S Army Medical Museum Neg No 65551)

man or the Wright stain In all except the developmental forms (Fig 17) the nucleus is centrally placed The characteristic kinetoplast is small and is usually found in the posterior part of the organism It is apparently composed of two parts the parabasal body and blepharoplast The flagellum is a hairlike structure that originates in the kinetoplast It either terminates at or extends beyond the anterior end of the parasite and in all except the leptomonad stages it is attached to an undulating membrane The flagellum acts as an anterior motor organ and should not be mistaken for a posterior tail In the flagellate stage the body of the trypanosome is elongated thin narrow flat and is frequently curved in the non flagellate stages it is round or ovoid The cytoplasm of the organism is generally finely granular or smooth and it may be vacuolated

Trypanosoma gambiense in man is polymorphic It may be long and narrow (Fig 18) intermediate thick stumpy or posteriorly nucleated The central location of the nucleus and the threadlike flagellum characterize the long narrow form The intermediate form is shorter and thicker its nucleus is centrally placed but it may not have a free flagellum The thick stumpy type is a more advanced form than the intermediate The posteriorly nucleated form is found only when infected blood is injected into laboratory animals it

differs from the advanced form only in the fact that the nucleus has moved posteriorly to a point in front of the kinetoplast

Trypanosoma rhodesiense (Fig 19) was discovered as a result of inoculat

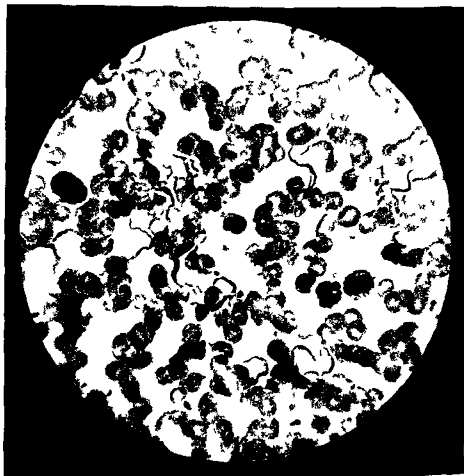


FIG 19 *Trypanosoma rhodesiense* Note the various forms of the parasite in a single field Photomicrograph × 970 slightly enlarged and retouched only to sharpen outlines (Leishm slide from London School of Tropical Medicine)

ing the blood of a man from Rhodesia into rats It was found to have forms in which the parasite was thick stumpy and non flagellated and had its nucleus situated posteriorly toward the kinetoplast Authorities differ regarding the differentiation of *T rhodesiense* from *T gambiense* In the 1935 edition of A Guide to Human Parasitology Blacklock and Southwell express the opin ion that there is no difference between the two parasites since no differential characteristics are possible in human blood and since *T gambiense* produces posterior nucleated forms when inoculated into laboratory animals

There are five developmental stages in the life cycle of the trypanosome (Fig 17) *Leishmania* and *Leishmanoids* are round or oval in shape and about half the size of a red blood corpuscle In these forms the kinetoplast is near the nucleus and both undulating membrane and flagellum are absent The *Leptomonas* stage is characterized by a slightly elongated body The process of elongation is yet further marked in the *Crithidia* stage The kinetoplast has moved and lies anterior to the nucleus A short undulating membrane and flagellum may or may not be present In the following stage the body of the organism is still more elongated the kinetoplast has moved to the posterior end an undulating membrane is present and there may be a flagellum

The *metacyclic* phase of the life cycle is found in the insect host The trypanosome that emerges from this cycle is smaller than that which develops in the human blood

Multiplication usually takes place by longitudinal fission The first stage of this process involves the division of the kinetoplast and the development of flagella from each divided section The nucleus divides into two following which the body divides on its long axis Each new organism contains one kinetoplast with its own flagellum and nucleus and the division continues until the new organism is connected to its parent at the tip only Complete separation then takes place

Mode of Transmission to Man Trypanosomes may be transmitted to man either by the cyclic process or by mechanical means In the case of *T gambiense* and *T rhodesiense* cyclic transmission takes place in the body of the insect vector the tsetse fly (*Glossina*) (Fig 20) Under natural conditions *T gambiense* is usually transmitted to man through the bite of infected *C palpalis* but *G morsitans G fusca G submorsitans G pallidipes* and *G tachinoides* are all listed by Craig and Faust as being capable of transmitting the flagellate experimentally *T rhodesiense* is transmitted ordinarily by the bite of infected *G morsitans* and in some regions by *C swynnertoni* (Craig and Faust 1937) The trypanosomes which the fly ingests in the course of an infective feed pass from the stomach to the hind part of the midgut Here they develop into long thin forms that usually have minute parabasal bodies A narrow undulating membrane is apparently formed and the lateral flagellum becomes closely attached to the body of the organism In ten days these organisms increase considerably in number They then make their way to the proventriculus where multiplication continues and then they pass forward to the hypopharynx and salivary glands The organisms appear in the salivary glands from twenty to thirty days after ingestion with the infective feed They are short and stumpy in appearance and when they reach the salivary glands the tsetse fly is infective to man

In addition to cyclic transmission the tsetse fly apparently plays a part in mechanical transmission as well since it carries the trypanosomes directly from one person to another This accounts for the spread of infection among people living in the same house Presumably the fly when interrupted in feeding on one individual attempts to resume its feeding on someone else but in the

process it transmits the infected blood that has adhered to its proboscis Mechanical transmission however is not limited to the tsetse fly Kellersberger observed instances in the Congo of the infection of whole families as a result

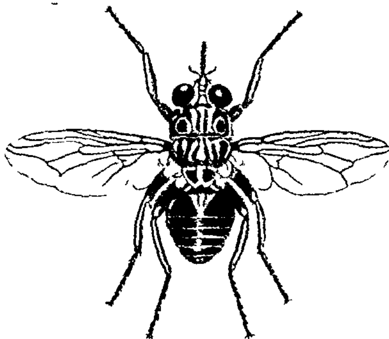


Fig 20 *Glossina palpalis* carrier of human trypanosomiasis (After Kolle and Wassermann)

of mechanical transmission by mosquitoes The mosquitoes evidently carried the infection from a trypanosomiasis patient to the other members of the families concerned Because the average native wears the minimum of clothing and most natives live and sleep in the same room conditions are favorable for the mechanical transmission of the disease by biting insects such as mosquitoes and bedbugs The effectiveness of this method of transmission depends on the length of time that trypanosomes can survive on the proboscis of the insect involved Some authorities believe that under the most favorable conditions they can survive for forty eight hours

PATHOLOGY

Trypanosomiasis caused by *T rhodesiense* is virulent and terminates fairly rapidly whereas the disease caused by *T gambiense* is less virulent and its course may be much longer and may not bring about the death of the patient for some years Otherwise the pathologic changes caused by the two varieties of trypanosome is essentially the same

Macroscopic The body may be emaciated but emaciation is not so much a characteristic of trypanosomiasis as a result of neglect or the inability of the

patient to eat properly The lymph glands are characteristically enlarged and may be visible or palpable in the neck and the groins The stage of enlargement is followed by further change in the course of which the soft glands shrink and become sclerosed The bronchial and mesenteric lymph glands are congested and may be hemorrhagic The organs of the body are pale the heart flabby and the liver and spleen may be slightly enlarged There may be congestion of the brain and the ventricular fluid may be increased in amount The cerebrospinal fluid is under increased pressure and is often turbid the dura mater is adherent in places and the pia mater is thickened

In some cases no gross changes are observed at autopsy

Microscopic In trypanosomiasis the inflammatory changes are primary and it is these which give rise to the parenchymatous changes The so called coat sleeve perivascular infiltration (Fig 18) of the meninges and the brain with small round cells is the most characteristic change observed The infiltrating cells are chiefly endothelial cells plasma cells lymphocytes macrophages containing ingested erythrocytes and proliferated neuroglial cells The lumina of the blood vessels are contracted and their walls are thickened Evidence may be found of polyadenitis as well as of chronic inflammation of the spinal cord and lymphatics of the brain Meningo encephalitis and meningo myelitis are also present There is proliferation of the lymphocytes and endothelial cells

Not only the meninges and brain but all organs also show round cell infiltration The condition is most marked in the lymph glands spleen and heart muscle There is actual invasion of the lymph glands by the trypanosomes In the lymph channels the infiltrating cells are more or less grouped in dense clumps but in the stroma of the organs they lie in small clusters Connective tissue may form in the lymph glands as a result of the cellular infiltration

Changes in the spinal cord are less marked than in the brain The lining of the central canal shows proliferation of the cells There are no changes in the peripheral nerve fibers In the later stages of the disease there is increased formation of fibrous tissue with thickening of the meninges and the adventitia of the blood vessels Lesions of the nervous system are due to actual invasion by the trypanosomes which have been found mainly in the frontal lobe of the brain tissue In the pons and medulla they can be demonstrated in masses or nests but they apparently have no definite relation to the blood vessels The parasites are often found in the spinal fluid

SYMPTOMATOLOGY

Incubation Period The bite of the infected *Glossina* is usually followed by a wheal or local inflammatory raised area about 1 to 2 cm in diameter This condition may last for several days before it gradually disappears From two to three weeks elapse between the bite and the appearance of trypanosomes in sufficient numbers in the blood to be found on an ordinary thick film If 10 cc of blood is citrated and centrifuged the parasites may be found earlier

Invasion The first symptom of the disease is the development of irregular

intermittent or of remittent temperatures of from 39 4 to 40 C (103 to 104 F) In white patients an erythematous rash appears at the same time as the fever This eruption is usually found on the chest and has the appearance of poorly defined pinkish areas ring shaped or crescentic in shape Although the rash is not readily seen on Negro patients it may be faintly visible Other symptoms include nervous excitement insomnia and prostration Headache is a common symptom and although it is not severe it may be persistent Neuralgic pains may appear in the legs and feet in addition to cramps in the calves of the legs Superficial and deep hyperesthesia is usually present so that a slight blow will produce sharp pain

Trypanosomiasis patients may be divided into two general groups dependent on whether or not there is invasion of the central nervous system and on the clinical appearance Examination of the cerebrospinal fluid in every case at the time the patient is first seen is of utmost importance in order to determine whether or not invasion of the central nervous system has taken place and also as a guide to future therapy If trypanosomes are in the circulation but the spinal fluid is normal only one course of therapy as a rule is necessary to cure the patient Spinal puncture should also be done at the completion of the treatment and repeated at intervals of about six months over a period of two years regardless of the stage of the disease at which the patient is first seen If there is involvement of the central nervous system as shown by the first spinal puncture and cerebrospinal fluid examination repeated courses of therapy with tryparsamide are indicated

Trypanosomiasis patients fall into one of three main clinical categories The *first group* includes those who are apparently in good health but who have trypanosomes in the blood stream It takes several weeks for the organism to give rise to symptoms and to multiply sufficiently to be found in the blood by ordinary methods Several months later the lymphatic glands especially those of the posterior triangle of the neck become engorged and enlarged At this time the trypanosomes may be found by gland puncture The typical so-called ganglion molle of the French may be present at this time or appear more fully later on in the second stage

The patients belonging to this group usually seek medical treatment for other conditions such as remittent fevers of a stubborn character chronic headaches or general ill health They do not suspect the nature of the disease from which they are suffering and sometimes refuse to accept the diagnosis But they are by far the most dangerous to public health since they constitute a fertile source of infection for hitherto uninfected flies that frequent springs bathing places river crossings and similar places In addition such patients may be the source of infection for biting insects in the mechanical transmission of the disease to whole groups of people

The *second group* of patients are those who show definite clinical symptoms They often volunteer the information that they go to sleep in the daytime It is especially significant if they sleep during the morning They have swollen glands in the neck constant headaches or irregular fevers Some complain

of sexual impotence or in the case of women of miscarriage of cessation of menses or of sterility Some patients complain of the sickness of sleeping The telltale expression of a certain intangible swollen stupid look is found



Fig 21 Sleeping sickness in a native of the B lgian Congo Note the typical facial e p ession

in this disease only (Fig 21) and is one of the most important features of the more advanced cases Examination of the skin reveals toward the end of the second stage of the disease a loss of its healthy shiny oily character The skin of patients at this stage turns a lighter shade of dirty brown Nervous symptoms also appear such as tremor of the tongue hands or whole body retarded movements slurred speech and a slow mental response Sometimes fear is evident or even mild mania Trypanosomes are less frequently found in the blood of patients belonging to this group but almost invariably there

are large soft glands in the neck the ganglion typique of the French and Belgians Other gland groups may also be enlarged In the Rhodesian type enlarged glands are not so constantly present



Fig 22 Sleeping sickness advanced stage in a native of the Belgian Congo

The second group of patients represent about 75 per cent of all those treated They are not as great a potential source of danger to others as the first group and although they are harder to cure they are easier to control since most of them realize the nature of their condition and seek help

The *third group* is composed of second group patients in an advanced stage of trypanosomiasis Many of these are practically abandoned by their people and are left to die alone in their villages They spend hours in stuporous sleep in filthy huts or out in the sun Their mania causes them to be driven into the forests or high grass where they fall victim to wild beasts if not to driver ants

The symptoms of this group are both varied and complex They fall asleep anywhere they are dull and they lie for hours (Fig ??) in a deathlike stupor in any position in which they happen to be They often go to sleep while sitting up and when they fail to conquer their stupor they sink down in a heap and lie in that position for hours No other symptom is so characteristic of trypanosomiasis as this stupor hence the name sleeping sickness The face is typically stupid speech and mentality are affected patients drool saliva there may be in co ordination or even paralysis Some patients border on insanity while others become insane and so must be restrained

The diagnosis is usually apparent Trypanosomes are as a rule not present in the blood and glands are usually shrunken and hard Gland puncture is difficult and negative in most cases Lumbar puncture together with the clinical symptoms is the most valuable aid to diagnosis in these patients The findings of the advanced second period are conspicuous in the later stage also but the symptoms and changes are all intensified In especially unfavor able cases the so called mulberry or muriform cell described by Dr Louise Pearce, is found and the globulin reaction is more strongly positive Death

is hastened by terminal diarrhea or by one of the complications such as malaria ankylostomiasis schistosomiasis or dysentery

COMPLICATIONS

The complications of African sleeping sickness include a terminal pneumonia diarrhea starvation Many of the unfortunate victims of the disease die of sheer neglect in the jungles Malaria ankylostomiasis schistosomiasis and dysentery are frequent complications The fact that these patients have sleeping sickness makes the complicating infections more serious

DIAGNOSIS

The diagnosis of trypanosomiasis depends on finding the parasites in the blood gland juice or spinal fluid In some of the clinically typical late or very advanced cases the parasite may not be found at all while the patient is alive

Blood Examination

(*a*) *Thick Films* Blood taken from the finger stained by the Giemsa or the Wright method and used as a thick film provides the most important and practical means of diagnosis in the first group of patients The parasites are relatively numerous in the blood stream during the invasion period which begins about three weeks after the initial bite by the infected tsetse fly and lasts for several months

(*b*) *Centrifugation* Add 1 cc of 3 per cent sodium citrate to 10 cc of blood and centrifuge this solution The method to follow is to centrifuge at about 1 000 revolutions per minute followed by 1 500 revolutions and continue this for about ten minutes A film made from the cells in the upper layer of the deposit may be examined fresh for motile trypanosomes or may be stained with the Giemsa stain or with one of the other Romanowsky modifications If this fails to reveal the parasites the supernatant fluid should be removed and centrifuged at 2 000 revolutions per minute for twenty minutes The sediment should then be examined

(*c*) *Blood Count* The blood count usually reveals leukocytosis with a preponderance of large mononuclear leukocytes A well stained film shows a clumping of the red cells This auto agglutination of the red blood cells is said to be constant and is suggestive of trypanosomiasis

Gland Puncture

Gland puncture with aspiration of gland juice is one of the most valuable of the diagnostic methods for the second stage of the disease when the glands are soft and swollen This method is positive in 87 7 per cent of cases Gland puncture should always be done at the same time as the thick blood film examination The enlarged glands may be unilateral or bilateral superficial or deep An ordinary hypodermic syringe and the needle usually used for intravenous injection are needed The typical gland juice aspirated is thick murky and it may be blood stained The gland juice is rich in lymphocytes and may

contain numerous parasites the activity of which will depend on the thickness of the lymph preparation and upon the time that has elapsed before examination The lymph preparation may be stained in the usual manner by the Giemsa method but in almost all cases the diagnosis is made with the fresh preparation which should be observed under a soft light and with the substage condenser reduced The soft dim light is important because the trypanosomes when unstained are practically transparent

Spinal Puncture

Examination of the cerebrospinal fluid is the only means of differentiating between those patients with central nervous system involvement and those without The character of the findings in the spinal fluid are of great help in determining the progress of the disease When there is involvement of the central nervous system the fluid is under increased pressure is more or less opaque and has an increased positive globulin reaction Lymphocytes may be increased to ⁿ ooo per cmm Centrifuging the fluid may possibly reveal the parasites

In those cases which respond favorably to therapy there is a rapid decrease in the number of cells as well as in the globulin reaction The presence of the so called mulberry cells is an unfavorable prognostic sign

Animal Inoculation

Animal inoculation into rats or guinea pigs with blood gland juice or spinal fluid is of assistance in establishing the diagnosis especially in the later stages when the parasites are scarce Blood films from the animals should be examined daily for a month or more in order to determine the development of the parasites

DIFFERENTIAL DIAGNOSIS

In practically all untreated cases trypanosomes are found at some stage of the disease The differential diagnosis of trypanosomiasis involves a study of the conditions associated with irregular fever such as kala azar malaria and such conditions as pellagra syphilis beriberi leprosy and Hodgkin s disease (Pel Ebstein fever) General paresis of the insane cerebral tumor meningitis encephalitis lethargica also have to be differentiated from trypanosomiasis

Malaria which is very frequently a concurrent disease is usually readily differentiated from trypanosomiasis by the demonstration of the *Plasmodia* in the blood smears Beriberi is non febrile whereas an irregular chronic fever is associated with trypanosomiasis Kala azar and the early stages of trypanosomiasis may be difficult to differentiate but the clinical symptoms of enlarged glands and local edema in the latter are clearly distinct from the symptomatic enlarged spleen and leukopenia of the former Examination of the blood and gland juice in the early stages also aids in establishing the diagnosis The cerebrospinal fluid examination is of greatest importance in all suspected cases especially late in the disease

PROGNOSIS

The prognosis of untreated trypanosomiasis is almost invariably fatal Those patients who are given adequate treatment in the early stages of the disease offer a good prognosis Cures in such patients have been remarkable Pregnant women who have been given suitable treatment have given birth to normal children

As a result of experience gained in the treatment of some 12 000 patients with trypanosomiasis Kellersberger has concluded that the so-called arsenic fast or antimony fast strains of trypanosomes involve in most instances only those patients who have not undergone adequate and regular therapy Other workers in the field believe the arsenic fast strains to be more common Although no authentic cases are recorded it is believed possible that a person may become infected with an arsenic fast strain of trypanosome from another individual who has not been adequately treated

TREATMENT

Trypanosomiasis is now a curable disease and is steadily being brought under control Formerly the outcome in untreated cases was almost universally fatal The most important factors in successful therapy of trypanosomiasis are the early recognition of the disease and the prompt institution of intensive therapy with adequate doses of one of the drugs known to kill the trypanosomes These drugs must be given over a sufficient length of time It is also important to diagnose and treat the numerous complications of trypanosomiasis and the ever present concurrent diseases In this connection the problems involved in malnutrition are particularly important It is impossible to stress too strongly the need for constant and vigorous treatment of patients with trypanosomiasis Such patients need the closest attention especially the further the disease is advanced and they respond in a remarkable manner to treatment Failure of therapy is usually due to reinfection to concurrent disease or to insufficient or especially irregular treatment

Tryparsamide and *Bayer 205* are the two most effective drugs in the treatment of trypanosomiasis The average dosages by intravenous injection are represented in Table II The dosages are for adults

Tryparsamide

Tryparsamide (the sodium salt of N phenylglycineamide p arsenid acid) cures trypanosomiasis in the early stages of the disease provided complications are not present It is also the only drug with therapeutic effect on patients with central nervous system involvement It clears the spinal fluid of large numbers of cells and as a result there is marked clinical improvement Over a period of seven years Kellersberger has treated 8 000 cases ranging from the initial trypanosome fever and rash to moribund cases and tryparsamide has invariably given the most satisfactory results The routine is to give fifteen injections at weekly intervals each dose being 0 015 gm per kg of body weight

TABLE II

DOSAGES OF TRYPARSAMIDE AND BAYER 205 IN TREATMENT OF TRYPANOSOMIASIS

	TRYPARSAMIDE	BAYER 205
Dosage per kg of body weight	0 045 gm *	0 02 gm
Total dosage depends on body weight and stage of disease	30–50 gm	5–10 gm
Dosage first injection	0 045 gm per kg †	1 gm (average) ‡
Interval of injections	Weekly	Weekly
Dosage on subsequent injection	0 045 gm per kg	0 5–1 gm
Total number of injections depending on stage of disease	15–20	5–10
Period of rest before repeating same drug or using other form of therapy	1 to 3 months	1 month

* Dosage for children up to twelve years of age is larger than for adults and is 0 08 gm per kg of body weight

† The precaution mentioned below also applies to tryparsamide but it is important that the drug be pushed to its tolerance as quickly as possible

‡ For initial infections a trial dose of 0 3–0 5 gm is preferable in an attempt to detect any idiosyncrasy to the drug Bayer 205 is then given on the first third tenth and thirteenth days after which it is given in weekly intervals and in the usual dose until the total amount is administered

In all cases of central nervous system involvement a second course must be given after a rest period varying from one to three months In advanced cases it is advisable to begin with a smaller dose in order to test the sensitivity of the patient The average first dose for these patients is 0 01° gm per kg of body weight The dosage is rapidly increased to full strength as the patient is able to tolerate the drug

Optic neuritis is found in some individuals who are sensitive to arsenical preparations such as tryparsamide The danger of blindness is greatest as the case becomes more advanced and approaches a fatal termination Blindness rarely comes on suddenly and in patients who are properly watched it is mostly transitory The premonitory symptoms are photophobia lacrimation pain in the eyes and dimness of vision The treatment for these symptoms is either to discontinue the drug temporarily or to lengthen the intervals between injections If care is exercised such symptoms will be rarely found Unfortunately the objective signs of eye damage are not always manifested early enough to prevent the development of blindness In some instances the action of the arsenic is delayed and the neuritis symptoms may develop after the cessation of therapy Arsenical dermatitis may also occur

Evidences of cure include the reduction of fever the normal cell count and albumin content of the spinal fluid and improvement in the patient s general condition Patients should return for examination at stated intervals usually from three to six months over a period of two years

Bayer 205

Bayer 205 (urea of acid dimeta aminobenzoyl meta aminoparamethyl benzoyl 1 napthylamino 4 6 8 trisulphonate of soda) is most effective in the early stages of the disease when the trypanosomes are circulating in the blood stream in large numbers It is given as a rule in 1 gm doses on the first third tenth and thirteenth days after which the injections are given at weekly intervals until a total dosage of 10 gm has been administered As with tryparsamide a smaller preliminary dose is administered to test the patient s sensitivity The drug is usually non toxic for man although albuminuria may develop as a result of kidney irritation In most cases this clears up within a few days but in the few cases in which the albuminuria persists treatment has to be discontinued Bayer 205 is one of the most active trypanocidal drugs known but its value is limited to the earlier cases It fails when used in the treatment of cases in which there is definite involvement of the central nervous system In such cases relapses have been frequent

Combined Bayer 205 and tryparsamide treatment has been tried as a result of the failure of Bayer 205 to cure all types of cases and its use has met with a certain degree of success

Other drugs which have been used in the treatment of trypanosomiasis include etharsanol and proparsanol each of which contains 20 per cent arsenic Both of these drugs cause optic injuries more readily than tryparsamide Neocryl is another arsenical that has been recommended but it also may induce arsenical poisoning and the consequent optic neuritis Atoxyl (soamin) was formerly extensively used but in addition to the disadvantages attached to the other arsenical preparations it also caused gastric irritation Tartar emetic (sodium or potassium antimony tartrate) has also been used in the treatment of trypanosomiasis

PROPHYLAXIS

Prevention of human trypanosomiasis involves not only protecting human beings from the bite of the tsetse fly but also protecting the tsetse fly from infection as a result of coming in contact with cases of the disease It also involves the eradication of the fly itself by destroying its breeding places

The *prevention of bites of the tsetse fly* is one of the most important factors in prevention of the disease The tsetse fly rarely bites about the face and neck thus the use of puttees and trousers to protect the legs from these flies is of great importance The tsetse fly bites only in the daytime If it is necessary to pass through a tsetse fly belt or locality inhabited by the flies it is best to do so at night The flies inhabit an area preferably close to the sides of a stream where they find the deep shade that is essential to the development of their pupae and young Therefore the underbrush should be cleared for about 30 yards on either side of streams and for the same distance or more around villages boat landings fords or other collections of water that afford shade for the flies If it is at all possible these areas should be avoided by human beings

Other measures aimed at eradication of the breeding places of the *Glossinae*

and destruction of the flies are of great importance Burning the grass and the use of the Harris fly trap have been suggested

The control of trypanosomiasis in Central Africa has been brought about largely through laying stress on the supervision of the people living in possible areas of infection Repeated and regular examination has been made of the whole population especially in heavily infected areas and for these people the possession of medical passports are obligatory Without such passports long journeys cannot be taken

All individuals who have trypanosomes in the blood or gland juice should be subjected immediately to medical supervision and should be given injections of either Bayer 205 or tryparsamide The systematic examination of the blood for parasites and the prompt treatment of those who are found to have been infected afford one of the most effective measures in the control of trypanosomiasis In addition if such treatment is instituted the rate of infection in the tsetse fly population will drop immediately Indeed if all human cases are properly treated the disease can be stamped out To this end the establishment of sleeping sickness centers and of dispensaries for the detection and treatment of new cases is of the greatest importance Natives have already discovered the value of curative drugs and are usually quite willing to co-operate with *medical authorities*

The injection of Bayer 205 as a prophylatic agent has been suggested but its value in preventing infection needs further confirmation

CHAPTER XIII

SOUTH AMERICAN TRYPANOSOMIASIS

Z T BERCOVITZ

SOUTH AMERICAN TRYPANOSOMIASIS (BRAZILIAN TRYPANOSOMIASIS schizotrypanosomiasis Chagas s disease) is an acute and chronic disease caused by *Trypanosoma cruzi* It is characterized by enlargement of the thyroid and the lymph glands by meningo encephalitis and by symptoms of thyroid and adrenal insufficiency Unlike African trypanosomiasis the South American disease involves children chiefly and the pathologic changes it produces result in the destruction of the endothelial and tissue cells of the body

HISTORICAL NOTE

In 1909 Chagas while on a malarial expedition in the northern part of Brazil found a cone nosed bug that was known as barbeiro It lived in the houses and after lights were out at night it came out to bite the natives who usually slept on the floor When Chagas studied these bugs he found flagellates of the *Crithidia* form in their hindgut He sent some of the bugs to the Oswaldo Cruz Institute in Rio de Janeiro where they infected monkeys Thereupon the monkeys developed trypanosomes in their blood Chagas then studied the bugs more closely and found that they were the intermediate hosts of the trypanosomes He found that the bugs could transmit the infection eight days after they had fed on infected monkeys

GEOGRAPHICAL DISTRIBUTION

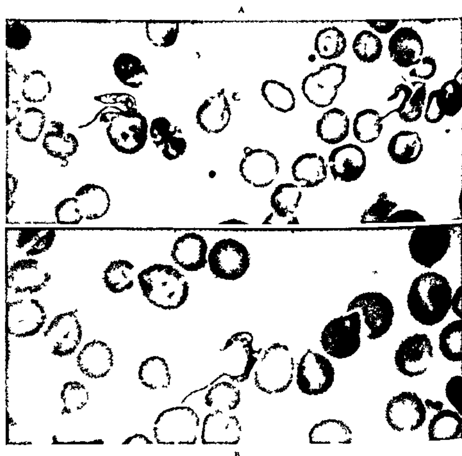
The infection is most prevalent in Venezuela San Salvador western Argentina and in Brazil in the provinces of Sao Paulo and Goyaz More recently it has been found also in Chile Peru Guatemala and Panama The geographical distribution of this disease has extended to the United States as shown by the work of Kofoid and McCulloch (quoted by Craig and Faust) So far no cases of Chagas s disease have been recognized in the United States

ETIOLOGY

T cruzi (Fig 23 and Plate XVI) has been proved to be the cause of a form of trypanosomiasis that occurs in parts of Brazil and in other areas of South

America as well as in Central America. In the human blood stream the parasite occurs as a typical trypanosome but in endothelial and some other tissues it occurs as a *Leishmania* form. In the developmental stages it probably occurs

A



B

Fig 23 *Trypanosoma cruzi* (3 forms) Photomicrograph × 970 slightly enlarged and retouched only to sharpen outlines (Teaching slide from London School of Tropical Medicine)

also as a *Leptomonas* and as a *Crithidia*. Morphologically *T cruzi* is distinguished by its C-shaped body which is about 20 microns long. Its nucleus is centrally placed and the kinetoplast is posteriorly situated. The kinetoplast which is probably the most striking feature of the organism is large and oval. The *Leishmania*-like bodies are found in the internal organs; they are about 4 microns in diameter, round or ovoid in shape, and have a nucleus and kinetoplast.

T cruzi has two life cycles, one in man and one in certain reduviid bugs. In man it does not multiply while it is in the blood stream. It invades endothelial cells or other tissue cells such as heart muscle, unstriped muscle, voluntary muscle, central nervous system, thyroid, suprarenals, bone marrow

and lungs where it sheds its flagellum and undulating membrane and so becomes the leishmanoid form It divides by binary fission a process which results in large numbers of *Leishmania* forms. These forms are then enclosed in a cystlike cavity in the cells that they have invaded Development continues with the production of *Leptomonas Crithidia* and *Trypanosoma* forms until at last the cell ruptures and liberates them Typical trypanosomes then appear in the peripheral blood and unless they are destroyed they are ready to repeat the life cycle

The life cycle in the *Triatoma megista* (*Panstrongylus megistus*) the reduviid bug begins when the host ingests the parasite while feeding on an infected individual The trypanosomes pass to the gut of the insect where they multiply by longitudinal division They develop into non infective *Crithidia* forms and later into metacyclic trypanosomes The bug expels them with its feces upon the skin of the person it bites and contamination of the wound that it makes with its bite gives rise to the infection The life cycle within the bug takes from ten to twenty days

Mode of Transmission to Man

T cruzi is transmitted from one individual to another by the reduviid bug *Triatoma megista* The method of transmission is by contamination with the feces of the bug which are rubbed into the bite These bugs defecate while they feed and the metacyclic trypanosomes which are discharged with the feces gain entry into the human system when the bite is rubbed or scratched In South America the reduviid bug *T megista* (*Panstrongylus megistus*) is the one that usually transmits the infection from man to man Craig and Faust list the following arthropods which have been proved to be capable of transmitting the infection *Eratyrus cuspidatus Eutriatoma sordida E uhleri Panstrongylus geniculatus Psammolestes coreodes Rhodnius pictipes R prolixus Triatoma brasiliensis T chagasi T dimidiata T infestans T protracta T rubrofasciata T sanguisuga* and *T vitticeps* The following bedbugs are listed by Craig and Faust as having been experimentally infected *Cimex boueti C hemiptera C herundinus* and *C lectularius* The following ticks are listed as being capable of being experimentally infected and transmitting the disease to laboratory animals *Amblyomma cajennense Ornithodoros moubata* and *Rhipicephalus sanguineus* In California Kofoid and Donat found that *Triatoma protracta* apparently transmitted the bug from animal to animal While in Arizona Kofoid and Whitaker (quoted by Craig and Faust) found *Eutriatoma uhleri* naturally infected with *T cruzi*

PATHOLOGY

T cruzi destroys the endothelial and other tissue cells in the human system The organism invades practically every organ of the body but it selects the heart muscle and neuroglial cells of the central nervous system for preference *Leishmania* like forms may be found inside the invaded cells

The gross pathologic appearance of the trypanosomiasis patient is that of a

PLATE XVI

THE TRYPANOSOMES AND ALLIED FLAGELLATES

A *Trypanosoma gambiense*
B *Trypanosoma brucei* (*T rhodesiense*)
C *Trypanosoma evansi*
D *Trypanosoma uniforme*
E *Trypanosoma caprae*
F *Trypanosoma vivax*
G *Trypanosoma simiae*
H *Trypanosoma congolense*
I *Trypanosoma equinum*
J *Trypanosoma equiperdum*
K *Trypanosoma cruzi*
L *Trypanosoma lewisi*
M *Trypanosoma theileri*

Various trypanosomes of man and animals × 2000 After various authors and originals (From Wenyon C M Protozoology Baillière Tindall & Cox)

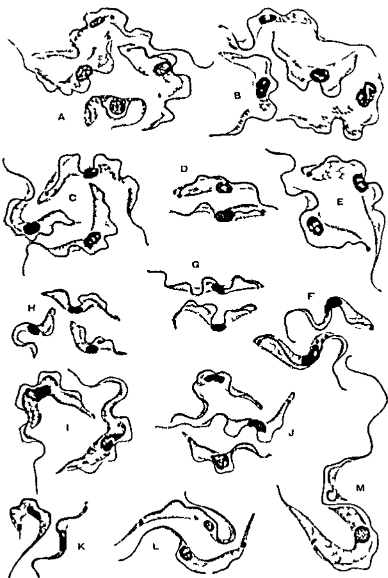


PLATE XVI

bronzing of the skin This is often accompanied by myxedema of the subcutaneous tissue The axillary and inguinal lymph glands are enlarged The thyroid gland which may be atrophied is enlarged and hard The mediastinal



Fig 24 *Trypanosoma cru i* in heart muscl (Courtesy U S Army Medical Museum)

lymph glands are also enlarged The pericardium is congested and may be hemorrhagic and the heart shows evidence of intense myocarditis The liver is fatty and enlarged while the spleen is congested and soft The mesenteric lymph glands are all enlarged The cerebrospinal fluid is increased in amount and the dura mater which adheres to the bone is congested The pia mater is thickened and edematous and a gelatinous exudate is found in the sub arachnoid space There are areas of meningitis and encephalitis

Microscopic The organisms are abundant within the muscle fibers of the heart (Fig 24) where they form cysts Following the rupture of a cyst the organisms are found free in the tissues In acute cases there is a diffuse inflam

matory reaction in the interstitial tissues while in the chronic cases there are localized areas of inflammatory reaction The small blood vessels of the heart show perivascular round cell infiltration Endocarditis and pericarditis may be present but no parasites are found in these lesions

The thyroid gland shows sclerosis and round cell infiltration but no parasites are found in this organ The liver shows marked fatty degeneration a condition that may be yet further intensified in acute cases The suprarenal glands are congested and fatty they show a marked inflammatory reaction to the presence of the parasites which are found both in the cortex and medulla of the glands

The central nervous system shows mild perivascular round cell infiltration similar to that found in African trypanosomiasis with scattered foci in the brain where the parasites are collected The neuroglial cells are filled with parasites which form cysts without causing a reaction around the cells When the cells rupture and release the parasites there are collections of mononuclear and polymorphonuclear cells to absorb them

The organisms invade the skeletal muscles especially of the legs arms and back As long as they remain in the muscle fibers there is no inflammatory reaction but when the fiber ruptures and the parasites escape an inflammatory reaction takes place around the area In addition there is perivascular round cell infiltration in the muscles

The testicles show inflammatory reactions to the invasion of the trypanosomes and the epithelial cells lining the seminal tubules also become infected with them Parasites may be found in the spermatozoa Round cell infiltration both of the interstitial tissue and around the blood vessels takes place

SYMPTOMATOLOGY

Chagas and his associates divided trypanosomiasis caused by *T cruzi* into acute and chronic forms according to their clinical pictures

The *acute form* usually affects infants under one year of age The disease is severe and the parasites may be found in the blood on direct examination The incubation period is about ten days and the onset is marked by fever which in severe cases may reach 40 C (104 F) The fever is continuous while the parasites are present in the blood stream but there may be slight morning remissions at times Early in the course of the disease the face becomes puffy and the skin crinkles like cellophane on palpation Conjunctivitis accompanies these changes The superficial lymph glands of the axilla and the inguinal regions as well as the thyroid gland are enlarged It is not certain however whether or not the enlargement of the thyroid is characteristic of trypanosomiasis for goiter is endemic in some areas of Brazil and consequently the thyroid involvement may be superimposed on the other disease Thyroid enlargement is one of the earliest symptoms to appear and it is chiefly observed in breast fed infants The liver and spleen are also enlarged Encephalitis and encephalo meningitis are terminal symptoms but the commonest cause of death is myocardial degeneration with heart failure caused by the invasion of the cardiac muscle with the parasites

Chagas further divided the acute form of the disease into two types

(1) Meningo-encephalitic type in which the nervous system is involved, resulting in idiocy paralysis and imbecility

(2) A type of the disease in which the nervous system is not involved

The acute form may last from ten to thirty days The child may die or the disease may assume the chronic form Spontaneous recovery does not according to Chagas take place at this stage of the disease

The *chronic form* in children may follow the acute form of the disease in adults it may assume this form from the onset Chagas distinguished five types of chronic trypanosomiasis

(1) The *pseudomyxedematous form* is the commonest form of the disease found in children up to fifteen years of age The symptoms include chronic cachexia irregular fever cardiac hypertrophy and tachycardia There is slight mucous infiltration of the subcutaneous tissues and the skin is bronzed The spleen liver and lymphatic glands are enlarged Convulsions may occur

(2) The *myxedematous form* is marked by definite solid mucous infiltration of the subcutaneous tissue mental deterioration arrested development and skeletal changes all of which are characteristic of myxedema The skin is dry and parchment like The lymph glands are enlarged and the thyroid gland is atrophied There are evidences of thyroid insufficiency Inflammation of the eyes and conjunctiva are common

(3) The *cardiac form* is marked by the presence of the trypanosomes in the heart muscle fibers Inflammatory reactions take place when the organisms are released from the fibers with consequent myocarditis Arrhythmia is an important symptom among children and extrasystole is often found among adults Heart block is common Death caused by asystole is a serious danger in this form of the disease

(4) The *nervous form* shows great variation of symptoms which depend on the particular areas of the brain that are invaded by the organisms Paralysis or spastic conditions of the lower extremities may result or the reflexes may be increased

(5) The *form with persistent acute and subacute manifestations* is marked by fever and other acute symptoms In adults this is usually the cardiac form together with enlarged thyroid and evidences of suprarenal insufficiency

DIAGNOSIS

In an endemic area enlarged thyroid gland myxedema bronzing of the skin irregular heart action and paralysis are suggestive of Chagas's disease *Malaria* must be differentiated by means of the blood examination *Hookworm disease* (ankylostomiasis) also must be excluded The nervous form of the disease must be differentiated from syphilis

LABORATORY DIAGNOSIS

In acute cases the trypanosomes are found in the blood in large numbers With the development of brain symptoms the number of trypanosomes *in*

creases in the circulating blood until death takes place When the disease as sumes the chronic form the trypanosomes decrease in number and are con sequently more difficult to find

T cruzi is very fragile and consequently it is difficult to obtain smears in which they are not torn To deal with this problem Tejera suggested mixing a few drops of blood with 10 per cent sodium citrate to prevent coagulation and then placing a small drop of the citrated blood on a clean slide where it could be exposed to the vapor of a ᵒ per cent osmic acid solution The blood is then smeared in the usual manner and stained In chronic cases the injection of from 5 to 10 cc of infected blood into a guinea pig or monkey is a suitable method of demonstrating the parasites It may be necessary to examine the endothelial cells of the capillaries of the lungs in the guinea pig to obtain the required information Mice and rats are not satisfactory for diagnostic injections because they often have *T lewisi* in their blood and these might be confused with *T cruzi* Postmortem diagnosis is made by examination of the heart muscle of the muscles of the legs and back and also of the brain

Complement fixation tests in the diagnosis of Chagas s disease have been devised and are practical and reliable These are of value especially since it is frequently impossible to demonstrate the *T cruzi* in the blood even dur ing the acute stage of the infection The preparation of the antigens and meth ods of carrying out the tests have been described in detail by Craig (1942)

The *culture* of *T cruzi* has also been accomplished Xenodiagnosis is a method described by *Brumpt in 1914* (quoted by Craig and Faust) in which laboratory bred triatomids are allowed to bite the individual suspected of having the disease If infection is present the trypanosomes multiply rapidly in the intestine of the bug and examination of the intestinal contents will result in their detection This method is successful when the trypanosomes are so few in number in the blood that they cannot be demonstrated micro scopically

COMPLICATIONS

There are no special complications other than those produced by the seri ous involvement of the heart suprarenals thyroid and brain

TREATMENT

No treatment is specific for this disease

PROPHYLAXIS

Prophylaxis depends on protecting individuals from the bites of the *Tria toma* and *Rhodnius* These insects are large and black in color The natives of the localities in which they occur know them well and call them barbeiros The nymphs can transmit the infection with their bites but the winged adult forms are more dangerous They bite at night when in search of blood which constitutes their food The armadillo is the reservoir host and other wild animals are also suspected of acting in this capacity Various forms of *Triatoma*

normally feed on the armadillo but when this animal leaves its burrow the bugs migrate to human habitations It is therefore important to build houses away from the burrows of the armadillos and also to construct the floors so that armadillos cannot burrow beneath them It is also important to construct the roofs of tile since the bugs will live in grass roofs but will shun tiles

Human beings should sleep under nets in beds that are so arranged that the bugs cannot crawl up the legs of the bed or along hammock ropes Travelers in endemic regions should avoid sleeping in native *habitations*

CHAPTER XIV

LEISHMANIASIS (KALA-AZAR)

Z T BERCOVITZ

LEISHMANIASIS IS A DISEASE CAUSED BY THE *LEISHMANIA* parasite Three clinical forms of the disease have been recognized namely kala azar (visceral leishmaniasis) which includes Indian kala azar infantile leishmaniasis and the post kala azar dermal leishmanoid oriental sore (cutaneous leishmaniasis) and American (mucocutaneous) leishmaniasis It is now believed that under the term visceral leishmaniasis may be included both Indian kala azar and infantile leishmaniasis which are either identical diseases or else closely related Post kala azar dermal leishmanoid occurs as a complication of visceral kala azar especially in those cases which have been treated with antimony compounds

Visceral leishmaniasis is a disease caused by the *Leishmania donovani* species of the parasite which involves the reticulo-endothelial system The condition is chronic in its course and characterized by irregular fever of long duration with enlargement of the spleen and liver emaciation anemia leukopenia and usually a fatal termination

HISTORICAL NOTE

In 1869 the attention of British officials in Assam was drawn to an endemic disease which decimated and in some cases almost wiped out the populations of the areas most seriously affected The natives called this disease kala azar (meaning black fever) because of the dark pigmentation that characterized the skin of those suffering from it

Leishman found what he thought to be degenerated trypanosomes in the spleen of a dead soldier and in 1903 he published an account of them In 1903 Donovan also found the parasites that Leishman had described in this case they were present in blood obtained by spleen puncture from a living patient In the same year Ross created the genus *Leishmania* and the parasite which caused kala azar became known as *L donovani*

EPIDEMIOLOGY

The devastating disease which the natives called kala azar and to which the attention of officials in Assam was directed in 1869 assumed epidemic

proportions It was found to travel slowly along the Brahmaputra valley taking about seven years to cover a hundred miles Natives moving from infected to uninfected villages took the disease with them and when once it was introduced to a new area it remained for six years or more before dying out The epidemic disappeared without apparent cause when it had run its course in any given locality Houses in which cases of kala azar occurred were regarded as unsafe for human habitation for at least a year afterward An epidemic of kala azar does not seem to run its course until all the people in the infected area have contracted it

GEOGRAPHICAL DISTRIBUTION

Kala azar appears sporadically as well as in epidemic form in India China the Mediterranean area and the Sudan In India at the present time it is mainly in Assam Bengal Bihar and Orissa and the United Provinces as far as Luck now Kala azar does not occur above an altitude of 4 000 feet In China kala azar is more common to the north of the Yangtse River In recent years the disease has been reported from various parts of South America Manson Bahr calls attention to the reports of the disease from Brazil Paraguay and Argentina

ETIOLOGY

Kala azar is caused by a parasite known as *Leishmania donovani* (Plate XVII page 2°4) This parasite is small with a rounded to oval body When oval in shape the size ranges from 1 to 3 microns in length by 1 5 to 2 5 microns in breadth The nucleus is usually faintly stained and has a parabasal body associated with it The cultural forms are leptomonads and do not occur in man In man it is found in an aflagellar stage only Species of *Leishmania* include *L donovani* *L tropica* and *L braziliensis* which are all almost identical morphologically *Leishmania* multiply rapidly by binary fission

L donovani as found in man is a small parasite rounded or ovoid in shape characterized by the presence of a relatively large vesicular nucleus and a rod shaped kinetoplast

L tropica cannot be distinguished morphologically from *L donovani* although according to Wenyon this species appears to have a greater range of size and shape than *L donovani*

L braziliense is morphologically identical with the other forms but in cultures it assumes a characteristic stumpy shape rather than the more elongated forms assumed by *L tropica* In spite of this distinction Wenyon prefers to identify *L braziliense* with *L tropica*

Location *Leishmania* organisms are cell parasites *L donovani* is found in the reticulo-endothelial system Occasionally it is found in other cells such as polymorphonuclear leukocytes and mononuclears in the peripheral circulation *L tropica* is found in the cytoplasm of macrophage cells Free forms of both species occur probably due to the rupture of the cells containing them

Size *Leishmania* are small Spherical forms measure from 1 to 3 microns

in length and from 1 5 to 2 5 microns in breadth Ovoid forms measure from to 5 microns in length and are about the same in breadth as the spherical forms

Shape *L donovani* forms are usually ovoid bodies although they may also be spherical The elongated torpedo forms are more rounded at one end than at the other Torpedo shaped forms occur frequently in *L tropica*

Ectoplasm A membrane usually definite envelopes the cytoplasm of the parasite

Endoplasm (cytoplasm) The endoplasm or cytoplasm stains pale blue with Wright preparations It is vacuolated and contains a large nucleus that is frequently flattened on one side and also a kinetoplast both of which are characteristic of the *Leishmania* parasite The kinetoplast stains reddish purple and is a rod shaped body pointing toward the nucleus It is made up of a rod shaped parabasal body and a blepharoplast The blepharoplast gives rise to an axoneme or rhizoplast which can be seen as a delicate red filament which extends from the kinetoplast to the margin of the ectoplasm The flagellum arising from the axoneme develops in cultures but not in man

For identification of the *Leishmania* parasite it is important to observe a sharply defined outline a large nucleus that stains pink or bright red and a more deeply staining rod shaped kinetoplast

Nucleus The relatively large spherical nucleus of the *Leishmania* parasite appears as a mass of granules that stain red in an ordinary dried smear With wet fixation and permanent stains however the nucleus is observed to have a membrane that encloses a clear space and a centrally placed spherical karyosome

Motility In cultures the oval or rounded forms are non motile They appear to be older forms that have rounded up and lost their motility

Mode of Transmission

The method of transmission of the parasite to the human host has not yet been determined It is presumed that some biting arthropoid is instrumental in introducing the parasite into the human system While evidence points strongly to *Phlebotomus argentipes* as the insect vector experiments have not yet established the fact that its bite is the only means by which kala azar is transmitted to man It is known however that when *P argentipes* bites an individual infected with kala azar it becomes infected itself with the parasite

The presence of *L donovani* in the intestinal mucosa was noted by Meleney Mackie Knowles and others including Shortt (quoted by Manson Bahr) who demonstrated the presence of Leishman Donovan bodies in numbers in blood and mucus stools in a boy suffering from kala azar with dysenteric symptoms and further showed that hamsters kept close together in a small cage contracted the infection from one another in the absence of an insect intermediary Forkner and Zia demonstrated the typical parasites in the nasal secretions in 12 (51 5 per cent) of 2 cases studied and smears from the pharyngeal tonsils of 10 kala azar patients showed parasites in 3 (30 per cent) They also

found the tonsillar tissue heavily infected with the parasite In another series of experiments Forkner and Zia showed that intraperitoneal inoculation into hamsters of nasal discharge from 14 patients proved that the parasites were present and had retained infectivity in 13 (92 8 per cent) These authors reviewed the literature both for and against transmission of kala azar by direct or indirect contact and by means of the bite of the sandfly They called attention to the fact that the literature on experimental kala azar contains numerous reports of the disease experimentally produced in animals by feeding infected tissue of man or animals or cultures of the parasite In one instance in man infection was believed to have been caused by accidental sucking into the mouth of infected material Forkner and Zia concluded patients with kala azar whether the symptoms of the disease are of short or long duration almost without exception have present in their oral and nasal discharges viable pathogenic *L donovani* Evidence is presented which strongly supports a theory of transmission of kala azar by means of direct or indirect contagion"

Life Cycle of Leishmania donovani

L donovani parasites have two known stages in their life cycle the aflagellar which takes place in man and the flagellar which occurs in cultures and in the *P argentipes* or sandfly

(*a*) *Cycle in Phlebotomus argentipes* The parasite invades the gut of the sandfly where it develops as a flagellate It multiplies rapidly and passes from the gut to the buccal cavity and the biting parts of the insect

(*b*) *Cycle in man* When an infective form of *L donovani* gains entrance to the human system it enters the reticulo endothelial cells and begins multiplying by binary fission This process of multiplication proceeds rapidly until it causes the rupture of the infected cells Then the parasites enter other reticulo-endothelial cells and begin multiplying once more The *L donovani* parasites are especially numerous in the spleen liver and bone marrow where they gather in the macrophages or histocytes

PATHOLOGY

The fundamental pathologic changes consist of infection of the reticulo-endothelial cells with the *L donovani* parasites The main changes are found in the spleen liver and bone marrow The intensity and duration of the disease apparently determine the extent to which other organs may become involved Marked emaciation characterizes the later stages of the disease

In untreated cases in man almost the entire splenic tissue may be replaced by large macrophages containing Leishman Donovan bodies The spleen is usually enlarged although in acute or very early cases it may not be enlarged clinically The liver may be enlarged though not to the same extent as the spleen The marrow in the long bones is dark red in color

The most important contribution to the histopathology of kala azar is that of Meleney in his study of the disease in the hamster (Fig 25) the monkey and in man The following is quoted from his conclusions The specific

tissue reaction to the infection consists of endothelial proliferation and the formation of solid masses of clasmatocyte tissue The liver spleen lymph nodes and bone marrow are the chief sites of formation of this tissue The

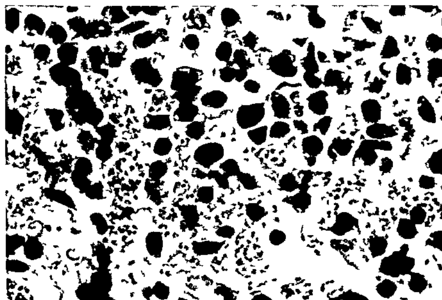


Fig 25 Leishman Do ovan bod es n macrophages (large mononuclear phagocytes) in spleen p lp of e perimentally nfected Ch nese hamster X 9 o (Cou rtesy of H nry E Meleney)

formation of tissue masses often appears to be in advance of the parasitization of individual cells

In the most advanced infections the parenchymatous cells of the liver and adrenal cortex become parasitized and severe degeneration of the liver occurs The spleen reaches huge proportions lesions appear in the kidneys and parasitized clasmatocytes appear in the connective tissue of practically all organs and tissues

In advanced infections the stroma of the intestinal mucosa is the site of massive accumulation of parasitized cells

Two human cases show practically the same histologic picture seen in experimental animals

SYMPTOMATOLOGY

The clinical symptoms of both Indian and infantile kala azar are very much the same Differences that may be noticed are mainly due to the fact that in the former the patient is usually an adult whereas in the latter the patient is frequently a child at times under one year of age Both types are characterized by the presence of prolonged irregular fever enlargement of the spleen and later of the liver also and anemia Both have very high mortality rates

PLATE XVII

Leishmania tropica and *Leishmania donovani*

Leishmania tropica and *L. donovani* from cases of oriental sore and kala azar Dried films stained with Romanowsky stains (× 2000)

1 Portion of a field in a smear from an oriental sore showing *L. tropica* scattered as a result of rupture of an endothelial cell

2 Detached portion of cytoplasm of endothelial cell showing *L. tropica* The outlines of the parasites are not visible Such bodies have been interpreted as schizonts

3 Red cell with superimposed *L. tropica*

4 Detached portion of cytoplasm of endothelial cell with *L. tropica*

5 Large endothelial cell packed with *L. tropica*

6 Three parasites (*L. tropica*) showing axonemes

7 Portion of a spleen smear showing *L. donovani*

8 Detached portion of cytoplasm of endothelial cell in peripheral blood film of kala azar case showing *L. donovani*

9 Large endothelial cell in peripheral blood film of kala azar case with a single parasite (*L. donovani*) in the cytoplasm

10 Group of nine parasites (*L. donovani*) in smear from cervical lymphatic gland of kala azar case

(From Wenyon C M Protozoology Courtesy of Baillière Tindall & Co)

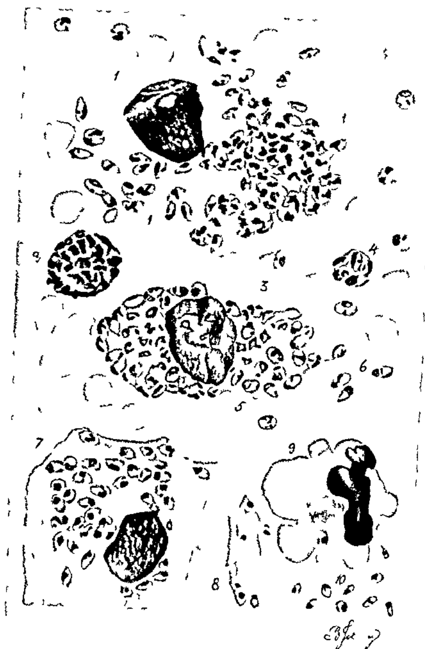


PLATE XVII

The onset of kala azar may be either gradual or sudden in the former case it is impossible to arrive at a clinical diagnosis from the symptoms observed When the onset is sudden the fever is high and it may follow rigor and severe gastric disturbance The fever may last from two to six weeks or more and its course may bear a close resemblance to that of undulant fever Moreover to complicate the clinical diagnosis yet further daily rigors may readily give rise to a suspicion of malaria

With the onset of fever the spleen and to a certain extent the liver may become enlarged There are some cases however in which the spleen and liver may not become clinically enlarged for some weeks even though the patients are ill with the disease Enlargement of the liver becomes more pronounced in later stages of the disease whereas enlargement of the spleen is a frequent symptom of the early stages At the same time marked enlargement of the spleen is not always an outstanding sign Cases of typical kala azar have been observed in which enlargement of the liver was the only symptom at first

An interval may follow in which fever is absent Subsequently however the symptoms return the fever recurs there is further enlargement of spleen and liver and there is frequently tenderness over these organs In women amenorrhea may also be an early symptom The symptoms gradually establish themselves and at length a fairly persistent but moderate degree of fever around 39 C (102 2 F) is present Remissions in the course of the fever are attended by profuse sweating The patient becomes anemic emaciated and after a time begins to show a characteristic picture of kala azar The skin becomes dark and grayish in color particularly on the hands feet and abdomen Hemorrhagic tendencies are noted in epistaxis and bleeding from the gums symptoms that are usually especially marked in infantile kala azar The hair becomes dry and brittle and in consequence may fall out

These symptoms may continue for months or for as long as two years Recovery may take place but the number of cases which recover is small Most cases terminate in death the immediate cause of which in 90 per cent of cases is some secondary infection

An important characteristic of kala azar symptoms is the fact that the patient s appetite is not impaired and his tongue remains clean In addition his fever is not attended by the usual symptoms of apathy and malaise and consequently he may be totally unaware of the fact that he has a fever

Leukopenia is by far the most important change in the blood There is a constant reduction in the number of leukocytes present in the blood stream and from the normal proportion of 1 white corpuscle to every 625 red corpuscles the count may fall to 1 to 2 000 or even 1 to 4 000 corpuscles or lower There are rarely over 3 000 leukocytes per cmm in the circulating blood and frequently 2 000 or less may be found when the disease has persisted for a month or more In the presence of complications leukocytosis may be present and the blood picture may become that which is typical of the complication There is also an increase in the number of monocytes The prognosis is un

favorable with low leukocyte counts Agranulocytosis is a serious complication in about 10 per cent of the cases

Relapses in kala azar are fairly common especially when the patient has not been adequately treated The relapse of kala azar is accompanied by fever and enlargement of the spleen Whenever fever recurs following a complete course of therapy in kala azar the differential diagnosis must be made of malaria and other conditions associated with fever

The criteria of cure in kala azar are difficult to determine in each case The patient may be considered as cured when the fever has been absent for a considerable period of time and there is a gain in weight with reduction in size of the spleen to within the costal margin and an increase in leukocytes Inability to find the parasites one month after completion of treatment is the best evidence of cure

COMPLICATIONS

Septic complications are commonly found in kala azar patients probably because of the changes in the blood which lower the resistance of the patient and make him more susceptible to secondary bacterial invasion These complications include pneumonia pleurisy cancrum oris cystitis otitis media mastoiditis herpes zoster cervical adenitis septicemia severe anemia and agranulocytosis Dysenteric symptoms are due to invasion of the intestine with the *L. donovani* parasite and secondary infection of the intestinal ulcers thus caused Post kala azar dermal leishmanoid is a complication that occurs

Malaria undulant fever and tuberculosis may be associated with kala azar but they are not complications of the disease

DIAGNOSIS

The clinical picture that indicates kala azar includes chronic irregular fever enlargement of the spleen emaciation and marked decrease in the number of leukocytes in the blood of patients living in or coming from districts where kala azar is endemic. The diagnosis can be established only on demonstration of the parasites of *L donovani* in the blood liver spleen or sternal bone marrow

The *L. donovani* occur in the leukocytes of the peripheral blood circulation but because of the marked decrease in the leukocyte elements of the blood they are difficult to find in the ordinary thin film Thick films are of value as is also the method of Shortt in which the spreading slide is quickly raised producing a straight-end film which is thicker than the balance of the smear Leukocytes are more numerous at this point This is then stained by Giemsa method and examined Five cubic centimeters of blood may be diluted with normal saline or Locke s solution thoroughly centrifuged and the sediment stained with Giemsa stain and examined According to Manson Bahr Young and Van Sant stated that the parasites are readily found by this method also that parasites appear from ten to twenty minutes after an injection of adrenalin solution

In those instances in which the examination of the blood fails to reveal the parasites they may sometimes be found by culture of the blood on Nicolle Novy and McNeal media No satisfactory growth develops before the seventh to the tenth day and the culture should not be discarded before three weeks

Aspiration of sternal bone marrow is considered by most authorities as the safest and most satisfactory method of diagnosis of kala azar Sternal puncture was originally recommended as a substitute for splenic and liver aspiration It is now considered to be as accurate and not as dangerous as splenic puncture Sternal puncture can be performed with a No 18 gauge spinal puncture needle and a 2 cc syringe The fluid thus obtained is expelled into a small tube containing from 2 to 3 mg potassium oxalate per cc after which it is examined for *L donovani* parasites Sternal puncture is a simple procedure which can be done repeatedly without any abnormal risk

Splenic puncture with aspiration of material from the pulp of that organ was used for many years as the most satisfactory method of obtaining material to demonstrate the presence of *L donovani* in patients with kala azar The best results are obtained when very little blood is withdrawn and more of the splenic pulp aspirated since it is within the cells of the spleen that the parasites are located It is important to note that this operation is dangerous especially when the spleen is soft and enlarged The slightest movement may cause a tear in the capsule or the puncture wound may continue to bleed in either case the patient may die This operation should be performed only by those familiar with the method and even then with the greatest care The addition of calcium lactate prior to splenic puncture has been recommended in order to promote coagulability of the blood The recent work with vitamin K may prove of value in preventing hemorrhage

Liver puncture is safer than splenic puncture but the parasites are more difficult to find than in material aspirated from the spleen On this operation it is best to attempt to secure liver cells rather than blood as the parasites lodge in the reticulo endothelial cells of the liver If blood is obtained it should be inoculated into culture media and attempts made to secure growth of the parasites

Laboratory Diagnostic Methods

Leishman Donovan bodies are found in blood films or in cultures made from the blood of individuals suffering from kala azar The parasites are usually found in the cytoplasm of reticulo-endothelial cells but they may be discovered in almost any organ of the body

When blood is withdrawn for the purpose of making blood films some should be taken at the same time for culture Parasites may be difficult to locate in the films whereas their presence will be more readily detected in culture

Blood Film Blood drawn from the spleen or liver should be stained with Wright s modification of the Romanowsky stains It may be necessary to examine many blood films before the typical leishmania forms can be found

Culture Cultures in the Nicolle Novy McNeal media are a recognized method of establishing diagnosis of leishmaniasis Material for culture can

be obtained from the spleen or from any other part of the reticulo endothelial system Best results are obtained when the hypodermic syringe is withdrawn as soon as blood appears above the needle for the endothelial cells will be more profuse in the material to be used for the culture

Developmental processes of the *Leishmania* can be observed when the material obtained by puncture is inserted in the cultural medium The parasite increases in size the nucleus develops and the cytoplasm becomes more vacuolated The flagellum begins to develop quickly after forty eight hours probably as an extension of the axoneme After this time flagellate forms may be seen in the cultural medium Many of these forms become elongated measuring as much as o microns in length while the flagellum is as long as or even longer than the body of the parasite Multiplication is by binary fission The parasites characteristically tend to cluster together in the culture with their flagella in the center and their bodies facing outward in rosette fashion As the culture begins to age the elongated or torpedo forms begin to assume an oval or rounded shape and to lose their flagella They also lose their motility

Serologic Tests Attempts have been made to find a diagnostic method by means of serologic tests though with variable or indifferent success

(*a*) *Napier s aldehyde test* For this test about 5 cc of blood should be withdrawn from a vein and should be allowed to stand until the serum is separated from the rest of the blood Then 1 cc of absolutely clear serum should be placed in a test tube and 1 drop of ,o per cent commercial formalin should be added This mixture should be shaken well and then placed in a rack at room temperature Solidification takes place in from three to twenty minutes According to Napier this jellification with opacity (resembling egg white) can be accepted as diagnostic of kala azar if the disease is of three or four months duration

(*b*) *Antimony test* Napier stated that this test was as valuable as the aldehyde test in the diagnosis of kala azar It is based on the observation that a 4 per cent solution of pentavalent antimony compound will produce a heavy precipitate when added to kala azar serum For this test one or two drops of blood from a finger should be allowed to fall into a tube in which 0 2, cc of per cent potassium acetate solution has been placed The contents of the tube should be mixed by inverting the container A little of the mixture should be poured into another tube and a 4 per cent solution of the pentavalent antimony compound should be allowed to trickle into this tube by means of a capillary pipette By trickling down the side of the tube the liquid will collect beneath the blood mixture In a case of kala azar a flocculent precipitate will form at once in advanced cases of the disease but it may take as long as fifteen minutes to form in new cases

DIFFERENTIAL DIAGNOSIS

Since the fever in kala azar has caused this disease to be confused with malaria a differential diagnosis is important Malarial *Plasmodia* will not be found on laboratory examination and clinically it will be observed that the

tertian and quartan periodicity of malaria will be absent while in treatment of kala azar quinine will prove valueless

As kala azar progresses dysenteric symptoms increase Consequently it is important to differentiate the condition present from that produced by either amebic or bacillary dysentery *L donovani* parasites may be found in scrapings from the ulcers in the large intestine when the symptoms are referable to a primary kala azar

Examination of smears made from the peripheral blood will eliminate leukemia In the case of infantile kala azar it is especially important to make this differential diagnosis and also to differentiate the blood in kala azar from that in the various anemias

No particular difficulty should be encountered in differentiating the condition from typhoid malignant endocarditis or Egyptian splenomegaly But it may be exceedingly difficult to establish a differential diagnosis between kala azar and trypanosomiasis unless the parasites can be found and their identity established

PROGNOSIS

The prognosis is now good except in cases which show severe intestinal disturbance or extreme leukopenia

TREATMENT

The pentavalent compounds of antimony used in treatment of kala azar include

(1) *Stibacetin* which was formerly used for the treatment of infantile kala azar but has now been superseded by other preparations

(2) *Stibosan* which has been extensively employed The initial dosage is 0 1 gm and the maximum dose is 0 3 gm The average case requires 7 5 gm of the compound although twice this quantity may be required if the case is particularly resistant Stibosan is obtained in ampules containing from 0 2 to 0 3 gm each The contents of these ampules should be dissolved in freshly distilled water in quantities of 1 cc of water to 0 05 gm of stibosan 2 cc for 0 1 gm and so on Injections of the solution can be given twice or three times a week and from eleven to fifteen injections are required For children fairly large doses of stibosan can be tolerated the maximum dose for three years of age is 0 1 gm and the initial dose 0 0 5 gm In the case of infants under two years of age intramuscular injections up to 0 1 gm can be given Stibosan should not be used if ascites is present and if jaundice should appear its use should be discontinued

(3) *Neostibosan* * which contains 40 per cent of metallic antimony is like stibosan relatively non toxic It is injected either intravenously or intramuscularly in 5 per cent strength doses The initial dose is 0 1 gm the second 0 2 gm the third 0 3 gm and so on until ten injections amounting to a total of from 2 7 to 4 0 gm has been given

* British equivalent is Neostam

(4) *Urea stibamine* which is a valuable preparation and sometimes succeeds when other preparations fail may be given as part of a combined treatment The dosage is the same as for stibosan and about 3 gm of the drug are required for a cure

(5) *Stibamine glucoside* (neostam) has also been recommended as highly efficient The following note is quoted from the Memoranda on Medical Diseases in Tropical and Subtropical Areas published by His Majesty's Stationary Office (London 1941) for the War Office For urea stibamine and stibamine glucoside Napier recommends 0 1 gm as an initial dose 0 2 gm as a second dose and 0 25 gm for each subsequent dose

Sodium and potassium tartrates of antimony are used in a per cent solution which is freshly prepared and administered intravenously This preparation is very toxic and should be used only when other preparations are not available and then with greatest caution The adult dosage is to start with cc of the solution (0 04 gm of the salts) and increase by 1 cc at each subsequent dosage *until a total of 5 cc is given on each administration The injections are made* every other day and continued until a total of 4 gm of the salt has been administered The dosage for children three years of age is 0 5 cc of a per cent solution increased to a maximum of cc For a child twelve years of age the initial dosage is 1 cc increased to a maximum of 3 5 cc The total curative dosage of the tartrates of antimony has been found to be about 4 gm for each 100 pounds of body weight In some instances 2 35 gm given in thirty injections seems to be sufficient but in others the full 4 gm given in forty five injections is required Such encouraging results were obtained with the intravenous injection of sodium antimony tartrate that further experimentation led to the development of less toxic pentavalent compounds of antimony which have proved a specific for kala azar

Toxic symptoms such as vomiting giddiness marked rise or fall in temperature rapid pulse and other signs of collapse call for a temporary suspension of the injections Improvement in the patient will be observed in the lessening of the emaciation the gradual return to normal size of the spleen and liver and the increase in the number of leukocytes in the blood stream The parasites cannot be regarded as completely exterminated until the spleen has gone back to its place within the costal margin

In addition to specific treatment directed to the eradication of the *L donovani* parasite from the system treatment of kala azar must be directed to the avoidance of secondary infections since these are responsible for much of the mortality with kala azar Tonics and nourishing diet should be given in order to build up the patient's strength

Treatment with pentavalent compounds of antimony has reduced the high mortality rate very considerably

PROPHYLAXIS

It is impossible to outline exact prophylactic measures in kala azar because the usual mode of transmission is not known Houses and localities

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CHAPTER XX

CUTANEOUS LEISHMANIASIS

HOWARD FOX

THERE ARE TWO TYPES OF CUTANEOUS LEISHMANIASIS which differ sufficiently to warrant their being considered as separate entities or at least as different varieties of the same disease The types in question are (1) oriental sore and (2) American or mucocutaneous leishmaniasis They will be discussed separately

Oriental sore (Aleppo boil Biskra button Delhi boil etc) is an infectious disease of wide extent in the Old World It is caused by *Leishmania tropica* which is either conveyed by the bite of some species of *Phlebotomus* or by personal contact It is a relatively harmless and usually self limited disease nearly always confined to the skin As a rule it disappears spontaneously within a year It is followed by permanent immunity It often leaves deforming scars on the face or the extremities

HISTORICAL NOTE

The disease has been known for many years having been described by Russel as early as 1756 and by others as a disease of Aleppo The organism was accurately described by J Homer Wright in 1903 under the name *Helcosoma tropicum* and was later recognized as a species of *Leishmania*

ETIOLOGY

The causative organism is a protozoan which morphologically and culturally is indistinguishable from that which causes kala azar (Plate XVII page 224) It is usually easy to demonstrate the organisms either in direct microscopic preparations or by culture except in the so called relapsing cases Material for examination is best obtained from the edge of a lesion (if ulcerated) or from the under surface of tissue removed for biopsy

EPIDEMIOLOGY

Oriental sore may occur at all ages in both sexes and in all races In large communities such as Aleppo and Bagdad the disease is said to be most often contracted between the ages of two and three years The disease also has a

known to be infected should be avoided Destruction of minute biting insects should be carried out The species of *Phlebotomus* thought to be the vector in kala azar are known to breed in moist dirt cracks and holes in the ground, among piles of rubbish and all kinds of refuse in old disused cellars and similar places They have been found in sides of drains low down near the foundations of walls Spraying these places with kerosene oil emulsion and whitewashing and ventilation are of value in prophylaxis

It has been reported that these flies are small and delicate and consequently they do not fly higher than about 10 feet Thus removal of patients to upper stories may be of value Napier notes also that *Phlebotomus argentipes* is very sensitive to smoke and is seldom found where cooking is done Periodic fumigation with sulphur cresol or crude tobacco has been recommended

Repellents such as camphor or ointments applied to the skin are of value at times A good ointment consists of oleum anisi oleum eucalypti oleum terbinth 3 minims of each in lanolin up to 1 ounce Mosquito nets with twenty two holes to the square inch are of value but such nets are uncomfortable if used at the time of the year that infection is likely to occur

It is of greatest importance that cases of kala azar should be regarded as infectious and properly isolated They should be especially protected from blood sucking arthropods In areas in which canine leishmaniasis occurs all infected dogs should be destroyed

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SYMPTOMATOLOGY

The incubation period is extremely variable and lasts from a few weeks to many months at times even more than a year The lesion is at first a tiny papule which gradually enlarges to form a plaque or button from 2 to 3 cm or occasionally from 6 to 8 cm in diameter Eventually it becomes soft and oozes a sticky material which dries and forms brownish adherent crusts When the crusts are removed an indolent ulcer with an edematous and pinkish areola is seen In some cases the lesions remain scaly and dry and do not break down to form ulcers When healing takes place a depressed scar is usually left which in many cases is more or less disfiguring The lesions may be single or multiple It is not uncommon to see two or three while in rare instances there may be 100 or more One case has been reported with 300 individual lesions

The favorite sites of oriental sore are the face and the extremities The disease is rarely seen on the trunk and never on the palms soles or hairy scalp The mucous membrane of the lip is occasionally affected

Oriental sore is a self limited disease undergoing spontaneous involution within a year in the great majority of cases This tendency of the disease is indicated by the Turkish name *habel seneh* or button of one year In a small minority of cases however the lesions persist for years and assume a tuberculoid structure histologically In other rare cases after apparent cure relapses occur and assume a tuberculoid structure Such cases last at times for decades and have until recently proved resistant to all treatment According to Berlin the relapsing type consists of flat round pinhead sized to lentil sized papules within the scars or in their immediate neighborhood As a rule one attack of oriental sore confers lasting immunity Oriental sore does not affect the general health and is practically devoid of both constitutional and subjective symptoms

COMPLICATIONS

There are no complications except frequent secondary pyogenic infection and more or less disfiguring scars

DIAGNOSIS

The clinical picture may be unusual as can be judged from many published illustrations An unequivocal diagnosis can be made only by finding the parasites either by direct microscopic examination or by culture In the relapsing (or tuberculoid) type it may be difficult or impossible to demonstrate the organisms In any case in which laboratory examinations are negative intracutaneous tests made from cultures of killed organisms may be useful Such tests are positive in a large proportion of cases

The differential diagnosis must be made from ecthyma syphilis tuberculosis blastomycosis lupus erythematosus tropical and other ulcers It may be said that the term Aleppo boil is misleading since at no stage do the lesions have the characteristics of an ordinary boil The term Biskra button is much more expressive and accurate

seasonal incidence occurring most often in tropical climates from September to January

Oriental sore is contracted either by direct contact with an infected person (or animal) or through an insect vector Both of these methods of infection have been definitely proved

Infection by contact has often occurred at the site of wounds or abrasions of the skin and in many families one member after another often develops the disease In certain communities it has been the practice to inoculate children on the arm or the body with the disease to forestall the inevitable scars on the face which follow natural infection *This is said to have been a former* custom of the Jews of Bagdad and of inhabitants of parts of Southern Russia Finally it should be added that various investigators have successfully inoculated themselves and other volunteers with cultures of *L tropica*

It has long been suspected that the disease might be carried by sandflies It has now been definitely shown by numerous investigators (Wenyon the Sergents Adler and others) that several species of *Phlebotomus* may act as vectors Other insects including the housefly may occasionally play the same rôle and may also at times transmit the disease mechanically Berberian proved that the stable fly may act in the same way

Dogs and monkeys (Macacus) can be easily inoculated and *it is well known* that dogs which frequently suffer from the disease naturally serve as a reservoir for the organisms It is also said that the brown bear of Turkestan plays the same rôle

Geographical Distribution Oriental sore is apparently limited to the Old World where it is endemic in many countries Its distribution in some regions coincides with that of kala azar though as a rule it is different The disease occurs in Africa Asia and parts of Europe In Africa it is common along the Mediterranean coast In Asia Minor it is especially common in Syria Palestine and Armenia It is also endemic in the southern and eastern parts of Asia including Iran Iraq India and parts of China In Europe it is found in Greece Italy Sicily Cyprus and Crete This incomplete list of endemic areas at least gives an idea of its wide extent The disease is occasionally seen in the United States and Canada in emigrants who have contracted it elsewhere Dwork recently published an account of twenty eight such cases

PATHOLOGY

L tropica is not a pyogenic organism the presence of pus in open lesions being due to secondary infection with ordinary pyogenic cocci The histologic structure in the early stage shows granulation tissue and perivascular infiltration Strong states that at times there is a striking appearance of focal accumulation of phagocytes which are swollen and contain large numbers of parasites According to Satenstein the structure is similar to that of blastomycosis except that in leishmaniasis there are more plasma cells scattered diffusely through the tissues and there are no micro abscesses in the epidermis In general the histologic picture is that of a granuloma without distinguishing characteristics

CHAPTER XVI

AMERICAN (MUCOCUTANEOUS) LEISHMANIASIS

HOWARD FOX

AMERICAN (MUCOCUTANEOUS) LEISHMANIASIS [BAURU ULcer Bahia ulcer (Brazil) espundia and uta (Peru) pian bois (French Guiana) forest yaws (British Guiana) and bosch yaws (Dutch Guiana) ear ulcer of the chicleros (Yucatan and Guatemala)] differs in some important respects from oriental sore It is confined to the New World and may affect the mucous membranes of the nose and throat at times causing severe mutilation and even death It is caused by an organism which is morphologically and culturally identical with those of kala azar and oriental sore The disease is chronic shows less tendency to spontaneous healing and responds more slowly to treatment than oriental sore does and healing may not be followed by permanent immunity

HISTORICAL NOTE

That the disease may have been known to the Incas of Peru is indicated by pottery on which are portrayed destructive lesions of the face suggestive of American leishmaniasis In 1909 the causative organism was discovered independently by Lindenberg and by Carini and Paranhos of Sao Paulo Brazil It was named *Leishmania bra iliensis* in 1911 by Vianna who in the same year introduced tartar emetic for the treatment of the disease The organism was first demonstrated in the so-called espundia type in Peru by Escomel in 1911 and in the uta type in 1913 by the Harvard commission led by Strong

ETIOLOGY

The disease is caused by *L bra iliensis* a protozoan which has the same morphologic and cultural characteristics as the protozoan which causes kala azar and oriental sore (page 2 0) It is found in the endothelial and large mononuclear cells of the affected areas of skin and mucous membranes and it is also free in the tissue spaces It is found less often in polymorphonuclear leukocytes It has not been observed in the peripheral blood The name *Leishmania bra iliensis* seems the most suitable one as the organism was discovered by Brazilian investigators and as the incidence of the disease is greatest in Brazil

PROGNOSIS

The prognosis as to life is invariably good In the great majority of cases the lesions heal satisfactorily

TREATMENT

In a disease like oriental sore which heals spontaneously it is at times difficult to evaluate any remedy As so many different methods of treatment have been advocated it would seem that there is no simple remedy which is invariably successful As the disease is not serious proper attention should be paid to cosmetic results especially when lesions are situated on the face

The lesions if few in number may be excised or destroyed by curetting electrodesiccation actual cautery or chemical escharotics Most of these methods however are likely to produce unnecessary scarring

Various remedies in the form of an ointment such as chrysarobin have been recommended to be used after removal of the crusts They have not proved satisfactory as a rule Various medicaments such as emetine and berberine sulphate have been used with success by injecting them into the base and border of the lesions Vaccine therapy has also been recommended using a saline suspension of washed heat killed flagellates

In the unusual cases in which the lesions are extremely numerous it seem advisable to try chemotherapy in the form of intravenous injections of tartar emetic

Physical therapeutic methods include the use of x ray ionization (with zinc chloride) solid carbon dioxide and recently grenz rays There is no doubt that excellent cosmetic results are often obtained by x rays but this agent is naturally expensive and its administration requires special technical knowledge Solid carbon dioxide has been highly recommended since it does not require elaborate apparatus is easily obtainable and gives quick and satisfactory results The so called grenz rays (x rays of 2 Angstrom units) have recently been used by Dostrovsky and Sagher in Palestine with excellent results These authors state that they have cured cases of the relapsing (tuberculoid) type which had hitherto resisted all methods of treatment including chemotherapy The average duration of treatment in all types of cases before a cure was obtained was from six to ten weeks There were no relapses in the 42 of their patients who were followed The total dosage of grenz rays given in the ordinary nodular or ulcerating types varied from 450 to 1 000 r In the relapsing cases it varied from 3 000 to 11 000 r

PROPHYLAXIS

Prophylactic treatment consists of personal hygiene and proper care of cuts and abrasions of the skin For protection against the bites of the *Phlebotomus* sleeping under nets which have forty five holes to the square inch and the use of insect repellents by day is recommended In endemic areas infected persons should be treated and advised to cover the lesions with dressings In areas where canine infection occurs the dogs should be destroyed

Leishmania can undergo a cycle of development and therefore it is suspected of transmitting the disease He concluded that circumstantial evidence indicates that American leishmaniasis is transmitted by a winged biting insect which lives among trees or shrubs He thought it probable that all forms of *Leishmania* are transmitted by the bites of certain species of *Phlebotomus* Aragao stated that there is often a close relationship to the bite of the *Phlebotomus* and the appearance of leishmaniasis and said that organisms similar to *Leishmania* have been found in the digestive tract of the sandfly The probability that sandflies usually transmit the disease does not exclude the possibility that it may be contracted by direct (or indirect) contact with open lesions It has been proved that the disease is autoinoculable

There is no known animal reservoir for American leishmaniasis It is true that on a few occasions the disease has been observed in dogs as a natural infection and at least in one instance in a horse This is in contrast with the frequency of natural infection in dogs by *L. tropica* American leishmaniasis has however been experimentally inoculated in dogs cats monkeys and guinea pigs according to Craig

GEOGRAPHICAL DISTRIBUTION

The name American leishmaniasis is appropriate as the disease occurs in North Central and South America In North America it is confined to the Yucatan peninsula especially the state of Campeche A few cases have been reported from Martinique though without confirmation In Central America the disease was first recognized in 1911 by Darling and Conner in Panama and has since been observed in Honduras Costa Rica and especially in Guatemala The greatest incidence by far is in South America where the disease has been observed in every country except Chile Its prevalence is greatest in Brazil especially the states of São Paulo and Bahia Next to Brazil it is most prevalent in Peru Paraguay and Bolivia

As in many other tropical diseases American leishmaniasis has numerous local names no less than twenty three of these being used in different parts of Latin America The term espundia is merely one of six local names in Peru As American leishmaniasis is of such wide extent it seems improper to designate it by a single local name espundia a term which is unknown to most of the natives of Brazil for instance and which is not used by the physicians of that country It seems as inconsistent as to call scabies the Philadelphia or Hong Kong itch

PATHOLOGY

The histopathologic picture of the cutaneous lesions is that of a non specific granuloma Biopsies from cases that I studied in São Paulo showed varying degrees of acanthosis and an infiltration of all types of cells which bore no characteristic relation to each other Tubercles and perivascular islands such as occur in syphilis were not observed There was vascular dilatation but not hyperplasia of the media

In spite of the rather striking differences in clinical manifestations between oriental sore and *American leishmaniasis* opinions differ as to whether *L braziliensis* should be considered a separate species or merely a variety of *Leishmania* Laveran and Nattan Larrier considered the organism to be a variety calling it *L tropica var Americana* Many however consider it a separate species The immunologic work of Noguchi in 19[illegible] appeared at the time to have adduced strong evidence in favor of the specificity of *L braziliensis* He inoculated rabbits with cultures of *L donovani L tropica* and *L braziliensis* and tested the immune serums for agglutination of cultures of their respective organisms He found that each immune serum agglutinated only its corresponding organism and concluded that there were three distinct species of *Leishmania* Noguchi s investigations were confirmed by Kligler but others failed to obtain similar results Complement fixation tests have not given any assistance and the question as to whether *L tropica* and *L braziliensis* are separate species has not been settled by serologic methods However Mayer and Ray showed characteristic differences in growth of the two organisms on a special solid medium and Geiman has recently observed cultural differences in growth on the chorio allantoic membrane of the chick embryo Cultures of *L tropica* were easily obtained remaining actively motile and capable of at least twenty six passages whereas *L braziliensis* lived only to the second passage

There has been considerable speculation as to the effect of other organisms growing in symbiosis with *L braziliensis* though this also occurs frequently in oriental sore Laveran suggested that the presence of bacteria in association with *L braziliensis* might account for the clinical features which are characteristic of the American type of the disease The presence of a gram positive diplococcus associated with *L braziliensis* was first observed by Seidelin In at least two cases the diplococcus was the only associated organism and in one case the skin was unbroken and there was no clinical evidence of secondary pyogenic infection

EPIDEMIOLOGY

American leishmaniasis may occur at any age in any race and in both sexes The great majority of cases are seen in men on account of their occupations Indeed the disease is largely an occupational one occurring especially among foresters workers on the tea plantations of Paraguay and those who collect chicle for chewing gum on the peninsula of Yucatan and in Guatemala The disease is most often contracted in moist tropical regions with virgin forests and luxuriant vegetation and especially during the rainy season Anderson however states that the so called uta type is seen in cold deep ravines on both the eastern and the western slopes of the Andes at altitudes of from 3 000 to 8 000 feet

The method of transmission of the disease is not definitely known though some species of *Phlebotomus* long has been suspected as the principal vector Shattuck in a study of the distribution of American leishmaniasis in relation to that of the *Phlebotomus* stated that this insect is the only arthropod in which

the fingers And this opinion is supported by the long interval which elapses between the cutaneous and the mucosal infections the latter often occurring after the cutaneous lesions have healed A similar view is expressed by Villele



Fig 26 American leishmaniasis in a Negro 15 year old showing large indolent ulcer of five years duration on the left leg and the scar of a healed ulcer on the right leg The nasal mucosa was also affected Observed in São Paulo Brazil (From H *Archives of Dermatology and Syphilology*)

who states that if the nasal infection is accepted as the primary focus it must be assumed that the *Phlebotomus* can feed inside the nose a fact that has never been demonstrated Against the metastatic theory are the absence of visceral lesions and the failure to find *Leishmaniae* in the blood

The following description of the mucosal lesions was given by Dr de Paula Santos in São Paulo The disease begins invariably in the mucous membrane of the anterior third of the nasal septum The nose is most often involved followed infrequently by the pharynx and less often by the larynx Rarely the tongue and the buccal mucosa are involved The disease begins with congestion which is followed by infiltration with a punctate granulomatous ap-

The histopathologic changes in the nasal lesions according to Klotz and Lindenberg consist of perivascular infiltration of lymphocytes in the submucosa with a gradual increase of plasma and endothelial cells forming nodules composed mainly of endothelial cells The nodules may undergo either necrosis or fibrosis Eventually endarteritis leads to extensive ulceration

SYMPTOMATOLOGY

The clinical forms of the disease may be divided into those which affect the skin alone and those which affect the mucous membranes of the nose and throat either alone or much more commonly in association with or following cutaneous lesions After the bite of a sandfly or some other traumatism or without apparent cause the affected part is said to become red and itchy or even vesiculate As a rule this stage is not seen by the physician until the disease is more advanced Eventually a papule or nodule forms which in the great majority of cases breaks down and ulcerates The lesions may be single or multiple and at times they are extremely numerous In 50 cases which I studied in São Paulo the average number of lesions was between three and four In one patient there were approximately 200 separate lesions The favorite sites of the disease are the exposed parts including the face arms and legs

The ulcers (Fig 26) are round or oval with well demarcated borders surrounded by a dull red edematous areola They are rather insensitive unless secondarily infected and have a scant seropurulent discharge They vary in size from that of large coins to that of the palm They may or may not be covered by crusts Eventually they heal and leave scars which are usually soft and pliable

However in severe or untreated cases of nasal involvement there may be decided mutilation of the skin about the nose and mouth The type of the disease which occurs among the laborers who collect chicle frequently causes considerable destruction of the auricle

In a minority of cases the nodules do not ulcerate Occasionally they become verrucous and suggest tuberculosis verrucosa cutis Rare types include those with a chain of nodules along the lymphatic vessels of an extremity and also the circinate and atrophic forms described by Escomel

The most striking clinical feature of American leishmaniasis is the tendency to involve the mucous membranes of the nose (Fig 27) and throat a condition which does not obtain in oriental sore This involvement is of serious import on account of its chronicity and destructive tendencies Statistics as to its frequency show that it occurs in from 10 to 20 per cent or more of all cases Da Silveira found the incidence of lesions of the mucous membranes of the nose throat and mouth to be 20 per cent of 15 000 cases observed in the state of São Paulo

The involvement of the mucous membranes according to Klotz and Lindenberg occurs from eight months to fifteen years after the appearance of cutaneous lesions In their opinion this extension of the disease is due to metastasis through the blood stream rather than to transfer of the parasites by

these cases This type of the disease resembles oriental sore in that it does not affect the mucous membranes but according to Escomel differs from it by not causing permanent immunity after healing



Fig 98 American leishmaniasis in a white man aged 30 The disease was confined to the lesion of the ear which was similar to the ear ulcer of the Chiclero Observed in São Paulo Brazil (Fox H [illegible] of Dermatology and Syphilology)

COMPLICATIONS AND SEQUELAE

When the disease is confined to the skin the only undesirable sequela is the scarring On the other hand when the nasopharyngeal tissues are involved and are not promptly treated severe scarring and mutilation may result Death from inanition may ensue in severe cases which have lasted for twenty or more years

DIAGNOSIS

A positive diagnosis can be made only by finding the parasites in smears (using Wright's or Giemsa's stain) or by culture It is apparently more difficult to demonstrate them in American leishmaniasis than in oriental sore Dr Oliveira da Fonseca of São Paulo expressed the opinion that it was easier to demonstrate the parasites in cultures than in smears or in microscopic sections In about 40 per cent of cases they could be obtained by culture

The intradermal test appears to be of considerable diagnostic value Montenegro who devised the test obtained positive reactions in 86 4 per cent of cases More recently Gomes obtained strongly or moderately positive reactions in 97 5 per cent and weakly positive reactions in 5 per cent of his cases The material used was a suspension in physiologic salt solution of washed flagellates with 0 4 per cent phenol used as a preservative

pearance Vegetation and superficial ulceration occur later the commonest types being the infiltrative vegetative and ulcerative At times there is atrophic rhinitis and rarely a verrucous type is observed



Fig 27 American leishmaniasis of eighteen months duration in an Indian aged 50 There was involvement of the nose lip pharynx and palate The lesion was practically healed following treatment Observed in Sao Paulo Brazil (Fox H *Archives of Dermatology and Syphilology*)

The nasopharyngeal manifestations of the American disease are totally unlike those of oriental sore Another clinical difference is the lessened tendency for the lesions of American leishmaniasis to heal spontaneously as compared with the usual definite self limitation of oriental sore Furthermore it is thought by some authors that immunity is not conferred by one attack whereas the opposite is true of nearly all cases of oriental sore

Why the type of the disease should vary in different parts of the Americas is not known For instance the chiclero ulcer (Fig 28) of the ear as previously mentioned is especially common in Yucatan and Guatemala whereas the serious mucocutaneous type is mostly seen in Brazil and Peru An unusual type of American leishmaniasis occurs on the slopes of the Andes in Peru where it is known as uta *Leishmaniae* have been demonstrated in some of

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In making a clinical diagnosis one must consider blastomycosis tertiary syphilis tuberculosis sporotrichosis and tropical ulcer The picture may be complicated by the associated presence of one of these diseases The nasopharyngeal lesions are to be differentiated from lupus vulgaris syphilis yaws rhinoscleroma nasal myiasis and leprosy A point in differentiation from blastomycosis when laboratory methods fail is that this disease does not yield to treatment with tartar emetic

PROGNOSIS

The prognosis as to life is invariably good in the pure cutaneous form and nearly always so in the mucocutaneous form if treatment is given In either case more or less scarring is inevitable

TREATMENT

Tartar emetic has been the drug of choice for treatment since its initial use for this disease in 1911 It has proved to be a specific remedy in most cases especially in those of the cutaneous type Some clinicians maintain that better results are obtained with fuadin a trivalent preparation of antimony which has the advantage that it may be administered intramuscularly All agree that the mucocutaneous lesions are much more resistant to treatment for such cases an arsenical preparation known as eparseno has been widely used in Brazil This drug is said to be the same as preparation No 592 in Ehrlich s series its cost however limits its use

PROPHYLAXIS

As the infection is thought to be due nearly always to the bite of the sandfly protective measures against this insect are of prime importance

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The Donovan body is a gram negative non motile encapsulated organism that reproduces in living tissue and only in large mononuclear endothelial cells Its method of reproduction is by multiple segmentation The virulence



Fig 29 Donovan bod es in smear from a pat nt th granuloma nguinale (Courtesy of Central Cl n c Bureau of S cial Hyg ene D p tment of Health City of Ne York)

of the organism is low Infection with the Donovan body does not lead to immunity for reinfections and superinfections have been observed

Most investigators have failed in their attempts to cultivate the Donovan body

Proof that the disease is sexual in character is seen in the fact that the site of the lesion is the genitals or adjacent parts also by the further observations that the disease has only rarely been described in children and that it is frequently found in prostitutes of the Negro race The organisms appear to be infective only to susceptible individuals or to those who have an actual break in the surface of the skin when exposed to the infection This inference is drawn from the observation that repeated exposure through coitus of normal individuals to those suffering from granuloma inguinale does not always lead to the infection of the healthy individuals with the disease The role of the pubic louse as vector for the agent (Butts) has not been proved

Granuloma inguinale has been reported from many tropical and subtropical countries such as India China Siam Malay States Australia the South Sea Is

CHAPTER XVII

GRANULOMA INGUINALE

HELEN OLLENDORFF CURTH

GRANULOMA INGUINALE (GRANULOMA VENEREUM ULcerating granuloma of the pudenda groin ulceration sclerotising granuloma scopulariopsis vénérienne) is a contagious chronic superficial serpiginous sclerosing granulomatous ulceration of the groin pubes genitals and anus It slowly extends peripherally and shows no tendency to spontaneous healing Apparently it is contracted through sexual intercourse

HISTORICAL NOTE

MacLeod in India in 1882 first described the disease under the name of serpiginous ulceration Later in 1896 Conyers and Daniels reported it the lupoid form of the so-called groin ulceration of British Guiana In 1905 Major C Donovan demonstrated organisms—subsequently named Donovan bodies—in scrapings of the cutaneous lesions Monkeys were successfully infected with the Donovan organisms by De Monbreun and Goodpasture in 1930 In 1938 Dienst Greenblatt and Sanderson reproduced granuloma inguinale experimentally in a Negro volunteer with an exudate which contained Donovan bodies but no other demonstrable organisms In 1939 Greenblatt Dienst Pund and Torpin again successfully infected three human beings with granuloma inguinale

ETIOLOGY EPIDEMIOLOGY AND GEOGRAPHICAL DISTRIBUTION

It is generally accepted that the Donovan body (Fig 29) which by the way is not related to the *Leishmania*—is the causative agent of granuloma inguinale but considerable difference of opinion exists as to its nature Many investigators believe that the Donovan body is an encapsulated gram negative bacillus (*Klebsiella granulomatis*) related to Friedlander s bacillus but this belief seems to have been disproved by the work of Greenblatt Dienst Pund and Torpin These authors advance evidence that indicates that the Donovan body is protozoan in nature *From its method of reproduction in mononuclear endo*thelial cells and from its growth requirements as well as from the clinical behavior of the disease they assume that the Donovan body is a sporozoan a view that Donovan himself held

The Donovan body appears as a small encapsulated body the nucleus of which resembles closely a small curved bacillus In extremely acute cases the organisms are not encapsulated and they can also be found extracellularly



Fig 50 Granuloma inguinale

The abundance of Donovan bodies varies They often fill vacuolated places in the plasma of the mononuclear cells and they are sometimes present in such large numbers that they completely obscure the structure of the cell The organisms can be stained in the tissues with Wright Giemsa or cresyl violet stains Investigators who are well versed in the technique will find Donovan bodies in 100 per cent of the cases Von Haam does not consider that other stains are made superfluous by the method of Lund and Greenblatt who demonstrated the organism by impregnation with a silver stain and who regard the affinity of the Donovan bodies for hematoxylin as characteristic

SYMPTOMATOLOGY

Granuloma inguinale begins a few days weeks or months after exposure as a small papule or pustule which becomes ulcerated at an early stage The lesion extends peripherally or by autoinoculation and when excoriated it is beefy red in color and bleeds easily The base of the ulceration is later covered with an abundant serous sero anguineous or seropurulent discharge that has an offensive odor As a result of the growth of vegetations a papillomatous fungating mass may be formed The borders of the lesion are irregular and serpiginous (Fig 50) The lesion extends rapidly when moist surfaces come into intimate contact one with another

lands Africa South and Central America It is now endemic and widespread in the United States In 19 6 Howard Fox collected data on 150 cases that had been reported in the United States including 15 cases of his own Investigation of cases in Birmingham Alabama revealed the fact that none of the patients there had been in the tropics A report from the Cleveland (Ohio) City Hospital which gave figures significant for Cleveland for the years from 19°3 to 1937 listed 67 new cases each of less than one year s duration

Although granuloma inguinale is most commonly found among Negroes the white race is not completely free from it The ratio in Fox s cases was 9 to 1 The persons affected are those with a specially low level of sexual habits

PATHOLOGY

In the center of the lesion the epidermis is absent It is replaced by serum fibrin and polymorphonuclear leukocytes together with a variable number of lymphocytes plasma cells and large mononuclear leukocytes This exudate extends to variable depths At the margin of the ulcer the epidermis is greatly thickened distorted and folded on itself This attempt of the epidermis to *overproduce gives the edge of the ulcer its everted elevated and* indurated appearance There is some infiltration of the epidermis with polymorphonuclear leukocytes and the pigment that is normally found in the basal cells—especially in those of Negroes—is missing The papillae of the epidermis which show decided proliferation penetrate downward into the papillary and reticular strata

The corium or subcutis shows a rather characteristic dense cellular infiltration composed chiefly of lymphocytes plasma cells polymorphonuclear leukocytes and fibroblasts Capillaries are numerous in the typical granulation tissue All the larger vessels show perivascular cellular infiltration There are no giant cells

Much sclerosing round cell infiltrated connective tissue is found in the later stages of the disease In these cell nests which are also found in the subcutis of hypertrophic lesions with extensive fibrous reaction numerous endothelial cells with encapsulated organisms may be seen These aggregations of cells indicate that an active process is going on in those areas In the cicatricial lesions the characteristic changes consist of thick bundles of a collagenous fibrous tissue often with foci that contain the organisms

The presence of numerous swollen mononuclear cells (endothelial phagocytes) containing large numbers of Donovan bodies is characteristic Pund and Greenblatt describe these cells in great detail Although some of the cells have only a single cyst most of them have from ten to twenty cysts Deep-staining bodies are grouped peripherally within the cyst The origin of this pathognomonic cell is doubtful It may be a histiocyte from fixed tissue an altered plasma cell or an endothelial leukocyte Pund and Greenblatt regard this cell as significant for granuloma inguinale as the Sternberg Reed cell is for Hodgkin s disease Schoch and Alexander however could not find this characteristic large cell in three definite cases of granuloma inguinale of the hypertrophic type

sepsis and death attribute the deterioration to secondary infection perhaps to fusospirochetosis

Thierfelder describes 6 cases in which initial granulomas of the genitals were followed by generalization of the infecting agent These cases belong to a group of 3 500 cases in New Guinea Mayer and da Rocha Lima quote Kuhn s and Hoffmann s cases in which generalization of the disease occurred with involvement of the bones liver and other visceral organs In the United States Becker reported a case of a blood borne systemic infection in which at autopsy lesions of granuloma inguinale were found in the intestinal tract and the ribs

After an interval of time which may be either short or long the chronic and ulcerative granulomatous process of granuloma inguinale may develop into squamous cell epithelioma (Lynch Greenblatt Sydenstricker and Pund Peck)

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of granuloma inguinale is made from the clinical appearance of the chronic granulomatous lesion of the genitals or neighboring areas with little or no involvement of the inguinal glands from the demonstration of Donovan bodies and from the response to treatment with antimony salts

Other venereal diseases often co exist with granuloma inguinale In each case of granuloma inguinale therefore a search is indicated for syphilis (dark field examination Wassermann) lymphogranuloma venereum (Frei test) chancroid (smear for Ducrey bacilli Ito Reenstierna skin test)

Clinically the disease must be distinguished from syphilis The beginning granuloma inguinale ulceration may simulate a syphilitic chancre (*Spirochaeta pallida* present) The condyloma like lesions of the anus may resemble secondary syphilitic condylomas The presence of spirochetes the positive Wassermann reaction and the involvement of the inguinal lymph nodes would establish the diagnosis of syphilis The older granulomatous lesions of granuloma inguinale may look similar to tertiary ulcerative gumma A positive Wassermann reaction and the response to antisyphilitic treatment however would decide the question

Chancroids are small acute lesions with undermined borders they contain Ducrey bacilli The Ito Reenstierna skin test is positive The inguinal bubo in chancroid is tender and tends to break down

Fox correctly points out that cases of phagedenic ulcerations were in reality granuloma inguinale

Lymphogranuloma venereum in its early stage has little in common with granuloma inguinale—except the confusing name Lymphogranuloma venereum seldom shows a primary lesion but if it does this lesion is small herpetic and transient Inguinal adenitis is a common feature in lymphogranuloma venereum In later stages the chronic enlargement of the external genitalia with excoriations and fistulas which are common to both diseases may cause one condition to simulate the other Rectal strictures will be found in esthi

Cicatrization of previously involved areas is striking New scar tissue breaks down easily In some cases the fibrous response is so extensive that hypertrophic lesions are formed In the beginning new scar tissue is devoid of pigment As a result large white scarred areas in the genital regions of Negroes are fairly characteristic of the disease Mutilation of the external genitalia is common

The disease involves the skin and mucous membranes but there is little pain or itching The course of granuloma inguinale is notably chronic

Granuloma inguinale is a disease of the skin and corium and not of the lymphatics Absence of enlargement of the neighboring lymph nodes in granuloma inguinale is noticeable If enlargement of the inguinal glands is encountered in the cour e of this disease it is due to secondary infection

Usually constitutional symptoms are absent However in prolonged or advanced cases anemia malaise loss of weight and general weakness are noted

Cases have been reported in which *extragenital* lesions coexisted with genital manifestations In these cases the skin of the body the lips the pharynx and the larynx were involved In many instances Donovan bodies were recovered from the extragenital lesions Robertson and Sharp described a case in which the extragenital primary lesions which had been contracted as a result of abnormal sexual practice were located on the cheek and lips

COMPLICATIONS AND SEQUELAE

In women granuloma inguinale may involve the cervix (Pund and Greenblatt) in the form of a granulomatous lesion or of a papillary mass simulatin carcinoma of the cervix Pund and Gotcher describe the symmetrical enlargement of the uterus the fibrosis of the tubes and the solid enlargement of the ovaries that were caused by granuloma inguinale and were seen at autopsy in a twenty eight year old Negress

In male patients phimosis with destruction of the prepuce and glans penis may occur Paraphimosis has been seen occasionally

As a result of cicatrization the lymph channels are sometimes blocked and pseudo elephantiasis of the genitals may occur In 14 of Fox s 150 cases a varying degree of elephantiasic enlargement of the genitals was recorded In some cases the scrotum may become hypertrophied the penis remains stationary and seems to be invaginated into the scrotum The picture may simulate esthiomène seen in lymphogranuloma venereum Rectal strictures are not encountered but anal strictures may result from involvement of the anus Urethral strictures may follow involvement of the urethra which in turn may lead to infection of the bladder and resultant septic cystitis

Necroses may lead to the loss of the penis and the scrotum or to deep destruction of the perineum and the anus Fistulas which naturally favor secondary infections may form

While in most cases the disease spreads along the surface of the skin in a few instances it leads to severe deep mutilating ulcerations which may expose the muscles of the bottom of the pelvis and may destroy the entire vulva Von Haam and D Aunoy who have observed cases of this kind which led to

trate solution intravenously One method of preparing the solution is to dissolve the antimony potassium tartrate in distilled water and then to boil the solution thoroughly Several authors are inclined to ascribe the comparative failure of the therapy to the boiling of the solution Untoward effects of the therapy such as headache dizziness nausea and vomiting are also ascribed to the same cause The tartrate solution should be sterilized by passage through a Berkefeld filter

Antimony potassium tartrate (tartar emetic) in ampules is given intravenously in a 1 per cent aqueous solution If possible it should be given on an empty stomach The dose starts with 3 to 5 cc twice weekly and it may be cautiously increased to doses of 10 cc

Fuadin which is a complex trivalent antimony compound is superior to tartar emetic and is well tolerated by patients who cannot take the tartar emetic. It is relatively non toxic Fuadin is given intramuscularly and the dose starts with 1 or 1 5 cc This can be gradually increased to from 3 to 5 cc The doses should be repeated every second or third day until twenty or twenty five injections have been given Response to this drug is noticeable in almost all cases

Anthiomaline (Merck) is a 16 per cent solution of lithium antimony thiomalate *

Randall recommended intravenous injections of triamide of antimony thioglycollic acid in 0 4 per cent solution or of sodium antimony thioglycollate in from 0 5 to 1 per cent solution Senear and Cornbleet saw decided improvement in a patient from intravenous injections of 0 4 per cent calcium thioglycollamide although relapse followed later

Injections of the antimony compounds should be given over periods of months and years They should be continued for several months after the lesions have healed first once weekly and later twice monthly to prevent recurrences

The first signs of improvement are lessening of the itching and the appearance or enlargement of islands of epithelial cells The injections cause cessation of the discharge progressive involution of the lesions and disappearance of the Donovan bodies

Roentgen rays in repeated doses of 1/4 erythema dose unfiltered (75 r) are successful in a few cases and of little value in others Some lesions have healed completely by this method of therapy alone In others in which antimony compounds had to be used as well it was thought possible that the roentgen rays broke down the sclerosing membrane and the connective tissue and that subsequent doses of antimony potassium tartrate were able to act on the causative organisms

For local treatment wet dressings with 1 8000 potassium permanganate for the odor and cauterization with silver nitrate to prevent excessive granulation are recommended

* Anthiomaline is of French origin and is not available in this country at the present time (1943)

omenc of lymphogranuloma venereum although they are not present in all cases The Frei test is positive and Donovan bodies are absent in lymphogranuloma venereum

Elephantiasis of the genitals occurs also in filariasis In the cases of filariasis larvae may be found in the peripheral blood or in the lymph and calcified larvae may be seen in roentgenograms

Papillomatous granuloma inguinale of the penis or anus may be confused with carcinoma The diagnosis will be determined by the histologic structure In some rare instances as already noted cases of papillomatous granuloma inguinale actually have developed into squamous cell epithelioma

Clinical Laboratory Diagnostic Methods

Repeated scrapings (not smears) should be taken with a scalpel from the periphery of the ulceration These scrapings are then stained with Wright or Giemsa stains Weidman suggests not leaving the slide too long in water when *following the technique for the Giemsa or other Romanowsky stains* lest the capsule become bleached If this should happen the Donovan bodies cannot be distinguished from diplococci In correctly prepared specimens the Donovan bodies appear as pink bodies (Fig 29) and resemble puffed rice It often happens that many slides with scrapings from the same lesion have to be examined before the characteristic organisms are discovered Failure to find the organism may be due to the limited numbers of Donovan bodies on the surface of the lesion to the fact that in their immature non encapsulated form the Donovan bodies may resemble and be mistaken for other organisms or to a superimposed infection which may be so overwhelming that it may obscure the presence of the Donovan bodies (Greenblatt Torpin and Pund)

Slides obtained from biopsy specimens are usually more satisfactory than those made with scrapings from the ulcerated process

McIntosh found the formol gel test positive in 14 out of 15 cases of granuloma inguinale The test is not specific for this disease

Complement fixation tests and allergic reactions in granuloma inguinale which have been studied by McIntosh and Peck have not been developed sufficiently so that they are satisfactory for clinical use

PROGNOSIS

In uncomplicated cases the prognosis is good However healing of the ulcerations may require a long time and may be accompanied by extensive scarring and mutilation of the external genitalia In generalized cases death from anemia may result

TREATMENT

Treatment of granuloma inguinale calls for the use of antimony compounds roentgen rays *local therapy and in a few cases surgery* Often one measure succeeds only to a certain point and for better results must be combined with or replaced by other methods

Aragao and Vianno in 1913 introduced the use of antimony potassium tar

trate solution intravenously One method of preparing the solution is to dissolve the antimony potassium tartrate in distilled water and then to boil the solution thoroughly Several authors are inclined to ascribe the comparative failure of the therapy to the boiling of the solution Untoward effects of the therapy such as headache dizziness nausea and vomiting are also ascribed to the same cause The tartrate solution should be sterilized by passage through a Berkefeld filter

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* Anthiomaline is of French origin and is not available in this country at the present time (1939)

Surgical treatment is recommended for cases of cauliflower like condylomas vulvar growth and severe elephantiasis

PROPHYLAXIS

Prevention is accomplished by avoidance of contact with individuals who are actually suffering from the disease or those with promiscuous sex habits

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SECTION THREE

DISEASES CAUSED BY SPIROCHETES AND SPIRILLA

CHAPTER XVIII

RELAPSING FEVERS

CHARLES FRANKLIN CRAIG

THE RELAPSING FEVERS (FEBRIS RECURRENS TICK FEVER louse fever famine fever spirochetal fever spirillum fever remittent fever spirochetosis) are a group of diseases that are caused by spirochetes and that are characterized clinically by relapses of fever at various intervals The infection is transmitted to man by lice and ticks the louse and tick transmitted fevers differing clinically in many respects Although numerous spirochetes have been identified by different authorities as causative agents of these fevers there is much confusion regarding the specificity of many of them Therefore it is most convenient at the present time to classify these fevers under two broad headings (1) those transmitted to man by lice and caused by *Borrelia recurrentis* and (2) those transmitted to man by ticks and caused by *Borrelia duttoni* These spirochetes have been placed in the genus *Spirochaeta* by some authorities and in the genus *Treponema* by others but the preferred classification now places them in the genus *Borrelia*

LOUSE-BORNE RELAPSING FEVER

Louse borne relapsing fever is an acute infectious disease—or perhaps a group of diseases—caused by *Borrelia recurrentis* or closely related spirochetes and transmitted from man to man by the body louse *Pediculus humanus* var *corporis* and probably also by the head louse *Pediculus humanus* var *capitis* The disease is characterized clinically by sudden onset and by two or more febrile attacks of from two to ten days duration with intervals between the attacks varying from two to twelve days Each attack terminates by crisis

HISTORICAL NOTE

The louse borne relapsing fever is the classical type apparently known to Hippocrates It was first accurately described by Craigie and Henderson who in 1843 called the disease relapsing fever In 1868 the spirochete was discovered in the blood of patients by Obermeier who named it *Spirochaeta obermeieri* In 1907 Mackie stated that the body louse transmitted the infection from man to man Sergent Nicolle and others corroborated this in 191

In 1913 investigation demonstrated the fact that lice transmitted the infection under natural conditions and that the infection was hereditary in lice

ETIOLOGY AND EPIDEMIOLOGY

The cause of louse transmitted relapsing fever is *Borrelia recurrentis* Other spirochetes such as *Spirochaeta novyi* have been described as the cause of louse transmitted type of relapsing fever in the United States But in view of the uncertainty regarding the specific nature of the different species of other spirochetes described as causative agents it seems best to regard the disease as caused by *B recurrentis* wherever it occurs

B recurrentis is a typical spiral organism It varies in length from 9 to 16 microns and in breadth from 0 3 to 0 4 micron The spirals or turns which vary in number from three to six are long and wavelike Sometimes two or even more spirochetes may be seen attached end to end producing forms measuring from 20 to 100 microns in length Motility is pronounced and is of an undulating and boring character Forms of the organism have been described within the red blood corpuscles but these were probably artefacts since *B recurrentis* is present normally only in the liquor sanguinis

B recurrentis may be stained with most of the stains employed in bacteriologic methods and with various modifications of the Romanowsky stain such as the Wright Leishman or Giemsa stains as well as with the Fontana stain In stained preparations no nucleus is visible but in preparations stained with the Wright stain chromatin granules can be seen distributed throughout the organism The extremities of the spirochete stain very poorly Very deeply stained granules which are scattered throughout the cytoplasm were once believed to be resistant forms but they are now thought to be degenerative in nature Reproduction takes place by transverse division and not by longitudinal division as was once believed Involution forms of the spirochete are sometimes observed but the most commonly observed forms show swelling along their course apparently caused by degeneration

The spirochetes (Fig 31) are found in the blood during the febrile paroxysms They are most numerous after the first two days and about forty eight hours before the crisis when dividing forms may then be numerous *B recurrentis* often disappears from the peripheral blood as long as thirty six hours before the crisis of a paroxysm During the afebrile periods it is usually impossible to demonstrate the organisms in the blood They decrease in number with each paroxysm of fever until it is necessary to employ thick blood films and animal inoculation to demonstrate them *B recurrentis* is also found in the cerebrospinal fluid

Noguchi (1912) who was the first to cultivate *B recurrentis* employed ascitic fluid containing citrated blood and a piece of kidney tissue Anaerobic cultivation is essential The spirochetes appear in large numbers in the cultures in from seven to ten days Since Noguchi s observations several authorities have cultivated this spirochete under anaerobic conditions on a variety of media

Immunity exists after an attack of louse borne relapsing fever and lasts for a limited period usually not longer than one or two years Immune bodies

that are specific for the particular strain of spirochete causing the infection are demonstrable in the blood of recovered patients This strain specificity has been used largely in differentiating the strains of spirochetes to which

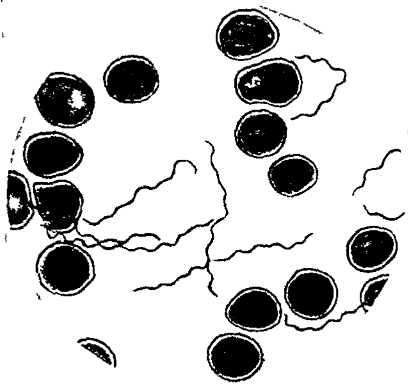


FIG 31 *Borrelia recurrentis* Wright's stain × 000 (Courtesy of U S Army Medical Museum)

specific names have been given and which have been identified as the causative agents of relapsing fever in different parts of the world but it is more than doubtful whether *species* can be separated on the basis of differences in such delicate serologic reactions alone and therefore it seems best to regard *these so called species as strains of either B recurrentis or B duttoni* Thus the spirochete of louse borne relapsing fevers in India known as *B carteri* and that in North America known as *B novyi* should be regarded as strains of the European species *B recurrentis* Morphologically all these different strains of spirochetes are identical

Transmission of *B recurrentis* from man to man takes place through the body louse *Pediculus humanus* var *corporis* and probably also through the head louse *Pediculus humanus* var *capitis* Infection is transmitted by crushing the infected louse into the bite or into an abrasion on the skin or by rub

bing its feces or coxal fluid into an abrasion on the skin The mucous membranes and the unbroken skin may also become infected Thus several cases have been recorded of individuals attending relapsing fever patients being infected through infected blood reaching the conjunctival membrane The fetus may be infected through the mother because the spirochetes are able to pass through the placenta

The morphology of the spirochete in the louse and in man is identical

Lice become infective in approximately sixteen days and remain infective for life It is maintained by some authorities that there is hereditary transmission of infection from louse to louse but apparently it is rarely observed Almost 50 per cent of the lice become infected after biting an infected individual

After ingestion by the louse the spirochetes disappear from the intestine in about twenty four hours They do not reappear for a period of from five to seven days when they may be found in the body cavity and eventually occur in enormous numbers in the coelomic fluid The form in which they are present in the louse after they disappear from the intestine is not known but Nicolle and his followers believe that there is an invisible stage in their development A granular stage of the spirochete in the louse has been described

Experimentally *B recurrentis* can be transmitted to the monkey rat and mouse The rabbit and guinea pig are infected only with great difficulty Nicolle and Anderson (1906) believe that rodents especially rats and mice may serve as natural reservoirs of infection for man

Louse borne relapsing fever appears whenever conditions favoring the propagation of lice are present The greatest number of cases is found when human resistance is reduced by overcrowding and other undesirable conditions produced by cold weather famine and war The disease is most prevalent among the poor classes and among those who neglect cleanliness In wartime this disease together with typhus is extremely prevalent The two infections may coexist in armies during cold weather when troops live in barracks or temporary shelters where sanitary arrangements are poor Under these conditions great epidemics of louse borne relapsing fever have occurred and the mortality may be high

GEOGRAPHICAL DISTRIBUTION

The geographical distribution of louse borne relapsing fever is restricted and the disease is now rarely observed in civilized communities that have good sanitation It is found throughout Europe especially in the Balkan countries and in Russia Asia certain parts of India Persia China Japan Indo China North and South Africa and Central America Epidemics have occurred in the United States but for a period of over twenty years louse borne relapsing fever has not been observed in this country

PATHOLOGY

The pathologic picture of relapsing fever is that of a septicemia At autopsy the skin may show petechial hemorrhages and jaundice The viscera appear

greatly congested hemorrhagic infarcts are present especially in the liver and the spleen both of which are enlarged and decreased in consistency Areas of necrosis may be present in these organs and fatty degeneration of the liver may be pronounced The kidneys are enlarged congested and may show the lesions of an acute nephritis The brain is much congested hemorrhagic areas may be present in the cortex The heart shows cloudy swelling The bone marrow is hyperemic and there is a great increase in the cells of the marrow *Spirochetes may be demonstrated in all the organs but they are especially* numerous in sections or smears of the spleen and liver within the reticulo endothelial cells of which they may be seen in large numbers They may also be seen in the reticulo-endothelial cells of the brain lymphatic glands and bone marrow

Early in the disease there is marked polymorphonuclear leukocytosis which is succeeded later by leukopenia An increase in the large mononuclear leukocytes can then be observed

SYMPTOMATOLOGY

The *incubation period* usually varies between three and six days but may sometimes be as long as twelve days or as short as two days In experimental infections the incubation period has varied between two and six days

The *onset* of louse borne relapsing fever is usually very sudden with chill severe headache dizziness pains and aching in the back arms and legs marked prostration and a rapidly rising temperature which usually reaches from 40 0 to 41 1 C (104 to 105 8 F) within twenty four hours Nausea and vomiting may be present Constipation is the rule although diarrhea may be present Convulsions are common in children The pulse is rapid varying between 115 and 130 per minute in usual infections and there may be symptoms of cardiac failure Delirium is sometimes observed There is complete loss of appetite Severe epigastric pain may be a pronounced symptom especially in children In a large proportion of cases symptoms of acute bronchitis are present More rarely iritis meningitis or acute nephritis complicate the clinical picture

The face is congested and jaundice may be present in cases in which fever has persisted for over a week The tongue is moist at first but later becomes dry and coated with a brownish fur During the febrile attack macular and petechial eruptions have been noted These are distributed over the trunk around the neck and on the inner side of the arms and legs In some infections isolated rose spots may also be seen on the trunk During the first day or two of fever an erythematous eruption may sometimes be seen on the trunk and extremities Skin eruptions however are not a common clinical feature of the infection and their absence is not evidence that the disease is not relapsing fever

The first or primary attack of fever (Fig 32) lasts for from three to six days sometimes longer the temperature is remittent in type and terminates by crisis In from 10 to 50 per cent of the cases of relapsing fever there may be

only one febrile paroxysm after which convalescence may begin About 25 to 65 per cent of the patients suffer one relapse about 20 per cent have two relapses and in only about 1 per cent are there more than two relapses

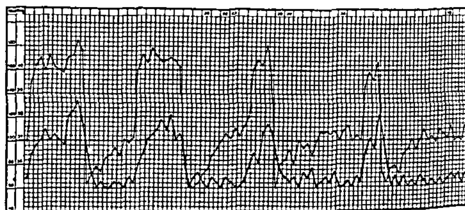


FIG 52 Temperature and pulse chart in a case of louse relapsing fever Note correlation of pulse and temperature (After Eggebrecht)

In the afebrile periods between the primary attack and the relapse the patient may feel perfectly well The length of this afebrile period varies with the duration of the fever it is longer when the febrile periods are short Thus if the febrile period is only three days the afebrile period will be about ten days while if the febrile period is eight days the afebrile period may be as short as five or six days The duration of the disease is from thirteen to sixteen days If several relapses occur the febrile periods tend to become shorter and the afebrile periods longer The symptoms during a relapse are similar to those of the primary febrile attack but they tend to become less severe with each relapse Prostration may be marked after a relapse but convalescence is usually rapid and uneventful

COMPLICATIONS AND SEQUELAE

Pneumonia either lobar or bronchial may be a complication Diarrhea or dysentery parotitis transient paralysis cardiac failure and in pregnant women abortion are other complications of this disease Owing to the great enlargement and softening of the spleen rupture of this organ has sometimes been observed Sequelae have not been noted

DIAGNOSIS

Clinical diagnosis of louse borne relapsing fever is based on the occurrence of a relapsing fever a history of infestation with lice and the presence of the characteristic symptoms that accompany the disease Mild cases are usually impossible to diagnose clinically and even severe infections are so often confused with other diseases that one should always rely on the demonstration of *B recurrentis* in making a diagnosis

Laboratory diagnosis of relapsing fever depends on the demonstration of *B recurrentis* in the blood or tissues of the patient either by darkfield examination or in stained smears of the blood if examined at the proper time Just before the crisis the organisms disappear from the peripheral blood and are absent during the afebrile period The spirochetes appear and disappear in the same sequence in each relapse

Darkfield examination of fresh blood is a very useful means of diagnosis and should be made if possible It makes possible a study of the motility of the organisms The India ink method is also useful This consists in mixing a drop of the patient s blood with a drop of India ink on a microscopic slide and then covering the preparation with a coverglass When examined with the high dry objective the spirochetes appear as refractile hyaline spiral bodies against the black background Thin blood smears stained with Wright Leishman or Giemsa stains and examined with an oil immersion lens or a high dry objective are usually successful if made at the proper time In doubtful cases it is well to examine stained thick blood films or smears made from centrifuged blood before resorting to animal inoculation Several smears should be examined before the result is considered negative because sometimes the spirochetes appear in very small numbers even during the periods when they are most apt to be numerous

The spirochetes may be demonstrated by the intraperitoneal inoculation of white rats with from 15 to 25 cc of the patient s blood If present they may be demonstrated in the blood of the inoculated animals in from six to eight days after inoculation

Differential diagnosis must be made between this infection and others such as dengue malaria yellow fever Weil s disease rat bite fever and typhus Careful attention to the clinical pictures and the employment of various laboratory methods should be sufficient to differentiate between relapsing fever and the diseases with which it may be confused In such differentiation reliance should be placed almost entirely on laboratory methods

PROGNOSIS

The prognosis in louse borne relapsing fever is usually good except in times of war or famine when the mortality may be very high The mortality has varied greatly in different epidemics from as low as 1 per cent to as high as 60 per cent but the usual mortality lies between 2 and 5 per cent in adults and about 5 per cent in young children The prognosis depends on the physical condition of the patient at the time of the attack his age the severity of the infection and the promptness and character of the treatment If treatment with one of the arsphenamines is instituted promptly the mortality should be practically nil except in greatly debilitated patients

TREATMENT

The patient should be kept in bed throughout the attack and for several days following the last relapse The bowels should be kept open symptoms

should be treated as they arise water should be given freely and the diet should be liquid and nutritious Vitamin C should be added to the diet and also other vitamins if the diet is deficient in them

Specific treatment of the relapsing fevers consists of the administration of the arsphenamines Salvarsan neoarsphenamine sulpharsphenamine and other arsenic compounds have been found effective The best method of treatment is by intravenous injections of neoarsphenamine administered in about two thirds the dose usually employed for syphilis The dosage should be very carefully correlated with the age and the weight of the patient None of the arsenicals should be administered if there is evidence of cardiac hepatic or renal disease Simple albuminuria is not considered a contraindication

It is important to remember that the *arsphenamines should never be administered just before the expected crisis* or at the time of the crisis since the liberation of large amounts of toxic material as a result of the destruction of the multitudes of spirochetes present in the body at these times may cause a fatal collapse The best time to administer the specific drugs is during the early hours of the primary and the relapse attacks

One intravenous injection of neoarsphenamine will usually cut short an attack but there is a relapse in approximately 40 per cent of cases unless further injections are given It has been found that depending on its severity from two to four intravenous injections are necessary to eliminate the infection

If for any reason it is impossible to administer the arsphenamines intravenously the use of acetarsone (stovarsol) is recommended for its high degree of effectiveness Acetarsone is administered orally in tablet form 0 3 gm (4 grains) being given five or six times a day The same precautions should be taken as with other arsenicals and the time of administration should be the same The gold compounds such as Solganol B have also been recommended by some other authorities but their value is not yet thoroughly established

PROPHYLAXIS

The prophylaxis in louse borne relapsing fever consists in delousing the patient and all contacts isolation of the patient and the protection of medical personnel with louse proof clothing Mass delousing is accomplished by superheated steam in either a stationary or a portable sterilizer the clothing being placed in the sterilizer and the individual should be given a hot bath his head should be shaved and clean clothing should be issued to him If head lice are present the scalp should be treated with a strong soapsuds kerosene emulsion half and half or with equal parts of crude petroleum and olive oil The mixture should be rubbed into the scalp after the hair is cut short and allowed to remain for several hours after which it is washed out with soap and water The eggs of the lice are combed out with a fine tooth comb Clothing may also be sterilized by dry heat at 60 C (140 F) for one half hour or by boiling If rooms are infested they may be disinfested by burning sulphur after they have been sealed according to the procedure followed in the disinfection of premises for bacterial disease Overcrowding should be avoided

because in crowds the lice are spread easily and rapidly from person to person

Vaccines prepared from cultures of *B recurrentis* have been tested for their prophylactic value Russian investigators have found that it is possible to produce immunity with the inoculation of dead cultures of this spirochete and this method of prevention deserves further trial The vaccine used by the Russians consisted of a mixture of primary and relapse spirochete strains that had lost their virulence

TICK-BORNE RELAPSING FEVER

Tick borne relapsing fever is an acute infectious disease or group of diseases caused by *Borrelia duttoni* or closely related spirochetes and transmitted from man to man by various species of ticks It is characterized by a sudden onset and by several febrile attacks which vary in duration and terminate by crisis

HISTORICAL NOTE

Tick borne relapsing fever was first described by Christy in 1903 in East Africa and the cause *B duttoni* by Ross and Milne in 1904 Dutton and Todd (1905) who studied the disease in the Congo discovered that it was transmitted from man to man by a tick *Ornithodoros moubata* Their work was subsequently confirmed by numerous investigators and much has been added to our knowledge of this infection in recent years

ETIOLOGY AND EPIDEMIOLOGY

The cause of tick borne relapsing fever is a spirochete called *B duttoni* and as in the case of louse borne relapsing fever several varieties of this spirochete are responsible for this type of relapsing fever in various parts of the world Although these variants have been given specific names they should be regarded simply as physiologic varieties of *B duttoni* since they are all identical morphologically Table III gives the names which have been applied to the varieties of this spirochete their geographical distribution and the names of the ticks involved in their transmission to man

The morphology of *B duttoni* is identical with that of *B recurrentis* The staining reactions are also identical Both organisms can also be cultivated upon the same media *B duttoni* has been successfully cultivated on the chorio-allantoic membrane of the chick embryo by the inoculation of defibrinated blood containing the organism Reproduction is by transverse division

Unlike *B recurrentis* the *B duttoni* organism is easily transmitted to a great variety of animals Guinea pigs rabbits rats mice dogs monkeys goats sheep squirrels bats hamsters and horses are all readily infected White rats or mice are the best laboratory animals to employ They can be infected either by inoculation with blood from patients or from infected animals or else by inoculation with the contents of infected ticks The reservoirs of infection for man are the burrowing rodents such as rats and mice Nicolle and Anderson (1927) were the first to state that this spirochete was found in many naturally infected

should be treated as they arise water should be given freely and the diet should be liquid and nutritious Vitamin C should be added to the diet and also other vitamins if the diet is deficient in them

Specific treatment of the relapsing fevers consists of the administration of the arsphenamines Salvarsan neoarsphenamine sulpharsphenamine and other arsenic compounds have been found effective The best method of treatment is by intravenous injections of neoarsphenamine administered in about two thirds the dose usually employed for syphilis The dosage should be very carefully correlated with the age and the weight of the patient None of the arsenicals should be administered if there is evidence of cardiac, hepatic or renal disease *Simple albuminuria is not considered a contraindication*

It is important to remember that the *arsphenamines should never be administered just before the expected crisis* or at the time of the crisis since the liberation of large amounts of toxic material as a result of the destruction of the multitudes of spirochetes present in the body at these times may cause a fatal collapse The best time to administer the specific drugs is during the early hours of the primary and the relapse attacks

One intravenous injection of neoarsphenamine will usually cut short an attack but there is a relapse in approximately 40 per cent of cases unless further injections are given It has been found that depending on its severity from two to four intravenous injections are necessary to eliminate the infection

If for any reason it is impossible to administer the arsphenamines intravenously the use of acetarsone (stovarsol) is recommended for its high degree of effectiveness Acetarsone is administered orally in tablet form 0 25 gm (4 grains) being given five or six times a day The same precautions should be taken as with other arsenicals and the time of administration should be the same The gold compounds such as Solganol B have also been recommended by *some other authorities but their value is not yet thoroughly* established

PROPHYLAXIS

The prophylaxis in louse borne relapsing fever consists in delousing the patient and all contacts isolation of the patient and the protection of medical personnel with louse proof clothing Mass delousing is accomplished by superheated steam in either a stationary or a portable sterilizer the clothing being placed in the sterilizer and the individual should be given a hot bath his head should be shaved and clean clothing should be issued to him If head lice are present the scalp should be treated with a strong soapsuds kerosene emulsion half and half or with equal parts of crude petroleum and olive oil The mixture should be rubbed into the scalp after the hair is cut short and allowed to remain for several hours after which it is washed out with soap and water The eggs of the lice are combed out with a fine tooth comb Clothing may also be sterilized by dry heat at 60 C (140 F) for one half hour or by boiling If rooms are infested they may be disinfested by burning sulphur after they have been sealed according to the procedure followed in the disinfection of premises for bacterial disease Overcrowding should be avoided

The development of the spirochete in the tick is not yet fully understood Most authorities agree that the organisms disappear from the digestive tract of the tick several days after it has bitten an infected individual although they may be found in the body cavity and organs of the body including the ovaries the coxal glands and reservoirs and in the salivary glands and the malpighian tubules The fact that the spirochetes cannot be demonstrated in the tick for some time after they disappear from the digestive tract except apparently in the form of granules has led to the theory that such a stage of development is essential However this theory has not been accepted by most students of the subject in spite of the fact that very short granular forms of the spirochete are present at certain times in the development of the organism in ticks Eventually the spirochetes reach the salivary glands and the coxal fluid and man may become infected either through the salivary secretion entering the wound made by bite of the tick or through scratching the secretion into an abrasion or into the wound made by the bite As a rule the infecting material is the coxal fluid containing the organisms which is exuded with the feces during the act of biting In some ticks transmission is wholly through the bite while in others both the bite and the coxal fluid are infective In Palestine Adler Theodor and Schieber (1937) proved that *Ornithodoros pallipes* did not pass coxal fluid while biting and that infection always resulted from the bite In the case of *O moubata* numerous observers have shown that infection may come either from the bite from contamination of abrasions or from the bite wound through the coxal fluid excreted while the tick is feeding It is also possible for the spirochetes to pass through the unbroken skin if they are rubbed into the surface Infection of man may also occur rarely from the blood of infected individuals being rubbed into an abrasion on the skin or even into the unbroken skin

Ticks do not pass from man to man as do lice Tick borne relapsing fever is a *place disease* because ticks do not travel for any great distance but remain in the region in which they are born Caves camp sites native shacks and definite areas of ground that may be tick infested will expose to infection all who enter them The ticks live on the ground or in the walls or floors of houses and they bite at night They will not bite if a light is present in the room but they can live for years without feeding during which time they are infective if they harbor the spirochete

The *geographical distribution* of tick borne relapsing fever is world wide but the *incidence of infection* is not nearly as high as in louse borne relapsing fever The disease occurs in Spain Portugal India Palestine Persia China Manchuria Morocco Tunis Abyssinia Somaliland Madagascar Eastern Central and Western Africa Cuba Mexico Panama Colombia Venezuela Peru Argentina Uruguay and in the United States in Texas California Wyoming Utah Arizona Kansas and Montana The tick borne type is never widely epidemic usually affecting small numbers of individuals who have become infected in camping sites or in native houses harboring infected ticks

TABLE III

TICKS TRANSMITTING RELAPSING FEVER

SPIROCHETE	GEOGRAPHICAL DISTRIBUTION	TRANSMITTING TICK
Borrelia duttoni	Tropical Africa	*Ornithodoros moubata*
Borrelia kochi	East Africa	*Ornithodoros moubata*
Borrelia rossi	East Africa	*Ornithodoros moubata* *Ornithodoros marocanus*
Borrelia hispanica var *marocana*	North Africa	*Ornithodoros erraticus*
Borrelia persica	Iran Northwest Asia	*Ornithodoros papillipes* *Ornithodoros lahorensis*
Borrelia hispanica	Spain and Morocco	*Ornithodoros erraticus* *Ornithodoros marocanus*
Borrelia venezuelensis	South and Central America	*Ornithodoros venezuelensis* *Ornithodoros talaje*
Borrelia neotropicalis	Panama	*Ornithodoros talaje*
Borrelia turicata	United States	*Ornithodoros hermsi* *Ornithodoros turicata*

rodents and that these animals acted as reservoirs of infection for ticks which in turn infected man It is believed today that tick borne relapsing fever is essentially an infection of rodents that is only accidentally transmitted to man

A more or less transient immunity is acquired after infection with *B duttoni* and immune bodies may be demonstrated in patients who have recovered from the infection During the first few days of the attack the spirochetes are found in the blood but they disappear some hours before the crisis and are absent during the periods between the relapses In the peripheral blood they are less numerous than in louse borne relapsing fever

B duttoni and its varieties are transmitted to man through the bites and the coxal fluid of infected ticks The exact species of vector concerned differs in different localities

Dutton and Todd in 1906 demonstrated that the form of relapsing fever found in Africa where they worked was transmitted from man to man by the bites of a tick *Ornithodoros moubata* and that the infection in the tick was hereditary The spirochete was found in the eggs of infected ticks and in the nymphs developing from the eggs fully explaining why tick borne relapsing fever is a typical place disease Ticks are very long lived and once they become infected they remain so for years and transmit the infection to their progeny Ticks have been found infected and able to transmit the spirochete for as long as four years after biting an infected individual

adopted are the same as those described for the laboratory diagnosis of *B. recurrentis* (page 263). Tick-borne relapsing fever must be differentiated from the same diseases as those already mentioned in the differentiation of louse-borne relapsing fever and similar methods of differential diagnosis should be employed (page 263). The spirochetes are less numerous in the blood than in the louse-borne relapsing fever.

PROGNOSIS

The prognosis of tick-borne relapsing fever is better than that of louse-borne relapsing fever, but in old and debilitated patients the mortality may be high. *The death rate is usually below 5 per cent, except in children, among whom it is higher.*

TREATMENT

What has already been stated regarding the treatment of louse-borne relapsing fever is equally applicable to that of the tick-borne varieties. The arsphenamines are specific, and of these neoarsphenamine is the arsenical of choice.

PROPHYLAXIS

The prophylaxis of tick-borne relapsing fever is quite different from that of the louse-borne type, owing to the difference in the transmitting agents. The tick vectors do not live in clothing but in the soil, the floors, and the walls of human habitations. Thus the avoidance of old camp sites and native houses in the endemic areas of the disease is an effective method of prophylaxis. The disinfestation of houses and camping grounds harboring the ticks should be carried out, if possible, but this measure is seldom practicable.

Bedsteads should be raised from the floor on smooth round legs which ticks cannot climb, and mosquito nets should be used over the beds. Native beds should be avoided and rest houses in infested districts should not be patronized. *As bedclothing frequently harbors the ticks, a careful inspection of mattresses,* sheets, and pillows should be made daily in tick-infested regions. Sleeping on the ground should never be practiced in such districts and, if possible, a light should be burned all night, since ticks will not bite in a lighted room. When building houses in tick-infested localities, builders should leave a space of at least one foot between the walls and the ground. Adobe or mud construction should be avoided, and floors should be made of cement.

There is no specific vaccine of value in the prevention of tick-borne relapsing fever, neither is there an effective skin repellent against ticks.

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PATHOLOGY

The pathology of tick borne relapsing fever is identical with that of the louse borne type (page 262) In both it has been found by study of experimental animals that the spirochetes may be demonstrated in the tissues of the

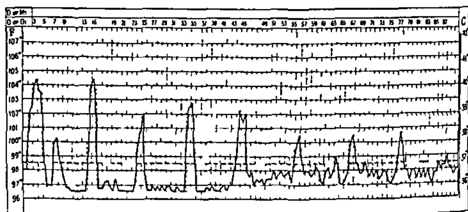


Fig 33 Temperature chart of untreated case of tick relapsing fever (After Manson and Thornton)

brain long after they have disappeared from other parts of the body Whether the same is true in human infection is not known although it is more than probable

SYMPTOMATOLOGY

The general symptomatology of the tick borne type of relapsing fever is similar to that of the louse borne type (page 63) However the fever (Fig 33) is usually higher and of shorter duration lasting as a rule from two to four days Relapses are more frequent the average number of periods of fever being from five to six while the disease periods are shorter averaging from seven to ten days Irregular types of temperature are much more frequent Sometimes an unexpected relapse will be missed and the next relapse will follow in twice the usual interval of time

COMPLICATIONS AND SEQUELAE

Complications are more frequent with tick borne relapsing fever than in the louse borne type Paralysis iritis dysentery and diarrhea cardiac failure and severe bronchitis are more often observed The tick borne type is much more frequently seen in children than the louse borne type and is more severe frequently resulting in death Sequelae are negligible

DIAGNOSIS

The diagnosis of tick borne relapsing fever depends on the demonstration of *B duttoni* in the affected individual The diagnostic methods which should be

CHAPTER XIX

INFECTIOUS JAUNDICE (WEIL'S DISEASE)

CHARLES FRANKLIN CRAIG

INFECTIOUS JAUNDICE (ICTERUS GRAVIS, ODAN-FKI (JAPANese), spirochaetosis icterohemorrhagica, leptospiral jaundice) is an endemic and epidemic febrile disease caused by the spirochete *Leptospira icterohaemorrhagiae*. It is characterized clinically by severe fever, prostration, jaundice and enlargement of the liver and more rarely of the spleen. The natural reservoirs of the infection are the rat and the mouse.

HISTORICAL NOTE

Weil in 1886 described a febrile disease characterized by jaundice and a considerable mortality rate. It has since been known as Weil's disease or infectious jaundice. In 1915 Inado and Ido demonstrated that the cause of the disease was a spirochete which they named *Spirochaeta icterohaemorrhagiae*. Their discovery was confirmed by Huebener and Reiter (1915) in Germany who called it *Spirochaeta nodosa*. The same spirochete was discovered independently in Germany by Uhlenhuth and Frome (1915) who called it *Spirochaeta icterogenes*. The organism really belongs to the genus *Leptospira* of the spirochetes and its proper name is *Leptospira icterohaemorrhagiae*. It is identical with the spirochete described by Noguchi as occurring in yellow fever and called *Leptospira icteroides*.

In 1917 the Japanese investigators found this spirochete in healthy rats and in the field vole and demonstrated that rodents acted as reservoirs of the infection for man.

ETIOLOGY AND EPIDEMIOLOGY

L. icterohaemorrhagiae is found in the blood, urine, sputum and cerebrospinal fluid of infected individuals. It is a closely wound spiral organism from 5 to 20 microns in length, the average length being from 7 to 12 microns, one end of which is usually hooked. It is very rapidly motile and the individual spirals are in such close apposition as to be invisible in the rapidly moving organism. With the darkfield the spiral structure is distinctly visible. This spirochete can be stained by the Wright, Giemsa, Leishman or Fontana stains

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During World War I under the conditions of trench warfare many cases of infectious jaundice occurred among the troops In France several epidemics occurred among the soldiers because large numbers of rats infected the water that was lying in the trenches in which the men were forced to stand for long periods of time

The following rodents have been found to be infected with *L icterohaemorrhagiae* in nature *Mus decumanus M alexandrinus M rattus Microtus montebelloi* and field mice belonging to the genus *Apodemus* Wild rats are the most important reservoirs and a considerable proportion of them is found to be infected in various localities Thus in London about 30 per cent harbored the organism (Stevenson 192) In Japan 3 per cent of wild rats and in Sumatra 6 per cent of normal dogs were found infected (Kowenaar and Wolf) Most laboratory animals appear to be immune to infection with *L icterohaemorrhagiae* but the guinea pig is especially susceptible for it is readily infected either by rubbing a little infective material into scarified skin or by percutaneous subcutaneous or intraperitoneal inoculation The infection in this animal is accompanied by typical pathologic changes of value in differential diagnosis (page 280) Dogs are susceptible to the infection and they sometimes transmit the disease to man Monkeys may also be infected if large amounts of infective material are employed but they may also be infected naturally An epidemic of infectious jaundice among chimpanzees in French Guinea has been described by Wilbert and Delorme (1927) who believed it was caused by this spirochete

The *geographical distribution* of infectious jaundice is world wide but it appears to occur most frequently in Japan During World War I numerous cases were reported in the armies operating in Europe Gallipoli Salonika and Egypt The disease occurs in the countries bordering on the Mediterranean in Germany Holland Belgium Russia in the Malay States and in the Andaman Islands Cases have been observed in England the United States Mexico Central America the Argentine Republic and Brazil In temperate regions the disease is most frequently observed in the summer It is usually of a milder type than that found in the tropics In Japan most cases occur during September and October

The *incidence* in Japan is high but in most other regions infectious jaundice is not a common disease

PATHOLOGY

Jaundice is a conspicuous finding for the skin sclerae and most of the organs are markedly jaundiced Hemorrhages are usually present especially in the fatty tissues and also in the lungs liver adrenals striated muscles and kidneys Edema of the tissues is generally marked The liver is increased in size and is frequently spotted with hemorrhagic or necrosed areas which give it a speckled appearance

Microscopically the liver shows fatty degeneration and necrosis the kidneys are characterized by marked acute nephritis with hemorrhages into the

Smears of blood or urine thus stained usually show the presence of the organism in small numbers It can be cultivated upon several culture media the most satisfactory being those of Noguchi Fletcher and Vervoort (page 280)

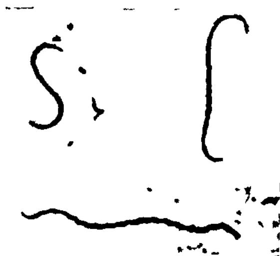


Fig 34 *Leptospira icterohaemorrhagiae* Giemsa stain × 3000 (After Noguchi)

Small numbers of *L icterohaemorrhagiae* (Fig 34) occur in the peripheral blood during the febrile period of the infection and also in the urine usually from the eighth day onward and according to some observers for as long as 100 days In very rare instances the spirochete can be demonstrated in the blood after the termination of the febrile period

Immunity A lasting immunity follows infection with this spirochete in man and immune bodies may be demonstrated in the blood serum as early as the end of the second week after the appearance of symptoms Agglutinins lysins and complement fixing antibodies may be demonstrated in the blood serum Uhlenhuth and Fromme (1918) found the blood serum still protective twenty two years after an attack of the infection

Rats are the natural reservoir of the infection and the spirochete is found in the kidneys urine and feces The rats are not themselves affected with the disease but they act as transmitters of the infection to man by contaminating food drink and bathing water and by their bites The spirochete has also been demonstrated in the slime of mines and sewers a finding which explains the fact that the disease is frequently observed in miners and workers in sewers In such cases it is believed that infection occurs through abrasions of the skin that have been contaminated by slime containing the spirochetes The polluted water of rivers and pools has also been found to contain this organism Epidemics of the disease have been traced to bathing in such pools In Holland and Germany the disease is most prevalent among such workers as farmers and miners whose occupations bring them into contact with water

fectious jaundice type which includes benign catarrhal long continued febrile meningeal pulmonary and nervous varieties

The onset is sudden with chills rapid rise in temperature marked headache and aching and pains in the muscles of the extremities and of the back Vomiting may occur and abdominal pain may be present The face is flushed the conjunctivae are markedly congested the cornea and sclerotic coat present a fine network of congested capillaries a symptom which some authorities consider almost diagnostic Prostration is very marked Pain in the muscles and bones may be so severe as to require an opiate

Jaundice occurs in over one half the cases and appears from the second to the fifth day following onset It is usually present from the second to the third day onward The jaundice may be accompanied by hemorrhages in the mucous membranes conjunctivae or skin and it may be very marked or else hardly discernible In the usual case the skin becomes lemon or dark orange in color but in very severe cases it may assume a mahogany hue Pruritus is marked in the more severe cases of jaundice but may be absent in those which show only a trace of jaundice Epistaxis and melena sometimes occur in severe infections and vomiting of blood resembling the black vomit of yellow fever is sometimes observed Nervous symptoms such as hyperesthesia delirium or somnolence are common in severe infections

The fever (Fig 36) is of the remittent type running between 39 and 40 C (102 2 to 104 F) It rises rapidly and attains its height in from twenty four to thirty six hours after which it remains remittent for a week to ten days when it falls usually by lysis There is customarily a secondary rise in temperature and during this time the spirochetes appear in the urine In the average case convalescence begins during the third week after the onset and is usually uneventful In mild infections the fever and other symptoms may subside within from three to five days In rare instances a third rise in temperature may occur after convalescence appears to have been established

Skin eruptions may occur in infectious jaundice During the early days of the attack petechiae are common later between the fourth and the tenth days an urticarial or measles like eruption may appear which may last for several days Erythematous and papular eruptions have also been noted Purpura occurs in the most severe infections and such cases are usually fatal

The liver is enlarged although not painful The spleen seldom shows clinical enlargement The gall bladder is tender enlarged and filled with bile The inguinal and axillary lymphatic glands are enlarged and tender and there may be general glandular enlargement In the meningeal type of infectious jaundice the cerebrospinal fluid is under increased pressure and the amount of albumin present in the fluid is increased Spirochetes are present in large numbers and may persist in the cerebrospinal fluid for several months after symptomatic recovery

The pulse is rapid at first but with the development of marked jaundice it becomes slow and the blood pressure decreases The urine is decreased in amount and contains albumin It is darker than normal but the color depends

tubules the spleen is soft and hemorrhagic the lungs may present hemorrhagic infarcts and the stomach and intestines reveal hemorrhages into the mucosa The lymphatic glands are enlarged and hemorrhagic. The fatty de

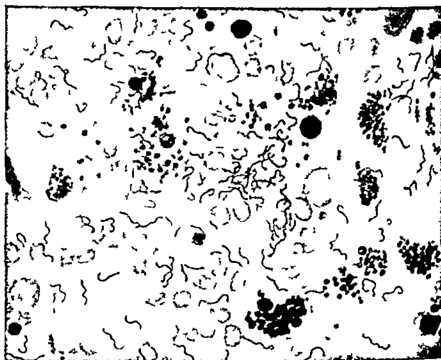


FIG 35 *Leptospira icterohaemorrhagiae* in a section of suprarenal gland Silver nitrate stain × 1000 (After Martin and Pettit)

generation of the liver in infectious jaundice although marked is not as extensive as in yellow fever or in acute yellow atrophy of the liver

The blood shows severe anemia the average count in a fatal case being below 3 000 000 erythrocytes per cmm There is also a marked reduction in the number of blood platelets and the coagulation time of the blood increases until it reaches twenty minutes in the usual infection

The cause of the lesions in infectious jaundice has not been determined since it has been impossible to demonstrate the presence of toxins The spirochetes (Fig 35) may be found in the tissues of the organs especially in the liver in sections stained with the silver impregnation methods such as Levaditi's method

SYMPTOMATOLOGY

The incubation period in infectious jaundice varies from five to twelve days usually from six to ten days Since the infection varies greatly in severity the symptomatology also varies The following types are recognized by Martin and Pettit (*a*) patients with very grave jaundice and (*b*) the classical in

on the degree of jaundice present In mild infections it is almost normal in color whereas in severe cases it is sometimes almost mahogany in color The amount of albumin present depends on the degree of jaundice varying from *a trace to large amounts in severe infections* Albuminuria usually *persists for* several days and the urine may contain besides bile epithelial casts and red blood corpuscles *L icterohaemorrhagiae* may be found in the urine during the later stage of the fever usually from the ninth or tenth day and may persist for several months having been found 120 days after the fever has subsided

At the beginning of the attack and during the first few days of fever (Fig 37) the blood count shows leukocytosis the polymorphonuclear leukocytes are increased and in addition there is a shift to the left in the Schilling count Later in the attack the leukocytosis disappears and there is an increase in the mononuclear leukocytes The red blood cells are decreased in number and the hemoglobin is likewise reduced

Relapses may occur after the third week but they are very rare

COMPLICATIONS AND SEQUELAE

Complications as pneumonia hematuria deafness pharyngitis iritis and *iridocyclitis are sometimes noted The sequelae include alopecia which is* not infrequently observed during convalescence anemia mental depression and general debility

DIAGNOSIS

The clinical diagnosis of infectious jaundice is possible in well marked cases of the disease but not in mild cases The sudden onset the character of the temperature curve the occurrence of jaundice and the albuminuria and the greatly congested conjunctivae are important symptoms in the clinical diagnosis of Weil s disease It should be remembered that identical symptoms occur in yellow fever and the differentiation of infectious jaundice from yellow fever is practically impossible without the aid of laboratory methods A clinical *diagnosis should always be supported by the demonstration of L icterohemorrhagiae* if possible

LABORATORY DIAGNOSIS

Guinea pig inoculation with either blood or urine is the most practical method and the one most commonly used in general practice During the first week of the infection the examination of the blood for *L icterohaemorrhagiae* may rarely be positive As the spirochetes occur in small numbers in the peripheral circulation about 5 cc of blood should be collected from a vein in the arm and should be centrifuged smears should be made from the sediment and should be stained with the Wright Giemsa or Fontana stains At the same time a darkfield examination should be made of preparations of the blood If the smears are negative the best method of diagnosis is the *percutaneous* subcutaneous or intraperitoneal inoculation of a guinea pig with the patient s blood Intraperitoneal inoculation of from 3 to 5 cc of the patient s blood is the method usually employed If the spirochete is present the guinea pig will

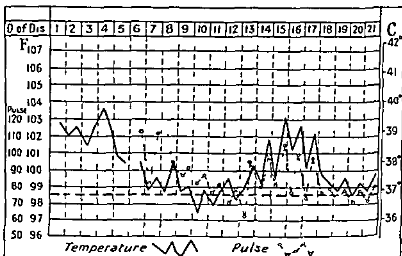


Fig 36 Temperature and pulse chart of a typical case of infectious jaundice (Weil's disease) showing the primary and secondary febrile attacks (After Inada)

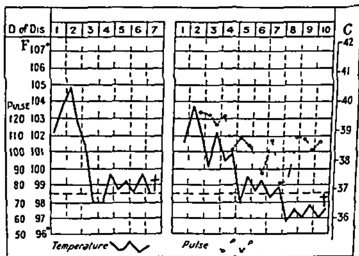


Fig 37 Temperature charts of two fatal cases of infectious jaundice (Weil's disease) Note unusually high pulse rate in second case (After Noguchi)

DIFFERENTIAL DIAGNOSIS

Infectious jaundice must be differentiated from yellow fever the relapsing fevers and certain malarial infections complicated by jaundice

Yellow fever resembles infectious jaundice in many cases so closely that clinical differentiation is impossible and diagnosis must depend on the use of laboratory tests The lack of correlation between the temperature and pulse known as Faget s sign in which a slow pulse is observed with a maximum temperature is characteristic of yellow fever This sign i not observed in in fectious jaundice although the pulse may be somewhat slowed in this disease if jaundice is pronounced

Injection of the blood of the patient into a guinea pig during the first week of the disease should determine the diagnosis for the guinea pig shows no symptoms after the injection of the blood of a yellow fever patient whereas if infectious jaundice is present the animal becomes jaundiced and usually dies within ten days During the convalescence of the patient the mouse protection test for yellow fever will demonstrate the nature of the infection If the patient has suffered from infectious jaundice the blood serum will not protect mice from infection with yellow fever

Some of the *relapsing fevers* may be mistaken for infectious jaundice and vice versa but the spirochetes are almost always demonstrable in the peripheral blood in the relapsing fevers whereas in infectious jaundice they are very rarely found

Certain *malarial fevers* in which jaundice is a complication may be confused with infectious jaundice but the examination of the blood for malarial *Plasmodia* should make a differential diagnosis possible Mild cases of dengue or phlebotomus fever may be confused with this disease but the presence of jaundice and a leukocytosis in infectious jaundice should serve as distinguishing symptoms Epidemics of a form of febrile nonspirochetal jaundice sometimes occur but such cases may be differentiated from acute infectious jaundice by the inoculation of a guinea pig as already described

PROGNOSIS

The prognosis of this disease varies considerably It appears to be much more fatal in some localities than in others In Japan the mortality has been as high as 50 per cent but the usual rate varies between 5 and 10 per cent It is more fatal in elderly individuals than in the young

TREATMENT

The arsphenamines although useful in other spirochetal infections are worthless in the treatment of acute infectious jaundice

Specific treatment consists in the prompt administration of an antiserum that is prepared by immunizing horses with cultures of *L icterohaemorrhagiae* The antiserum is administered intravenously usually at intervals of several hours according to the severity of the infection and should be continued for three

exhibit a rise in temperature within twenty four hours This persists until the death of the animal which usually occurs within a week or ten days Toward the end of the infection marked jaundice develops the animal becoming bright lemon yellow in color Albumin casts and red blood corpuscles appear in the urine and hemorrhages from the nose anus or female genitalia occur after the first three or four days of the disease *L icterohaemorrhagiae* may be demonstrated in both the blood and urine of the infected guinea pig At autopsy the pathologic lesions characteristic of infectious jaundice will be found to be present Smears from the spleen and liver should be positive for the spirochete

Cultures of the blood of patients suffering from this disease may be employed in diagnosis These cultures are often successful if proper media are used. During the first week of the infection the blood should be cultured but for cultures made later than the first week urine will give the best results The Fletcher Noguchi Lindenberg and Vervoort media have been found most useful The Fletcher medium consists of 5 cc of distilled water or sterile tap water 0 5 cc of a melted 2 5 per cent agar and 1 cc of rabbit blood serum in each culture tube The Noguchi Lindenberg medium consists of 800 parts normal saline solution 100 parts fresh rabbit blood serum 100 parts per cent agar pH 7 0 and 10 to 20 parts of rabbit hemoglobin solution made by adding 1 part of defibrinated rabbit s blood to 3 parts of distilled water The Vervoort medium consists of a solution of 0 1 per cent peptone and of 0 05 per cent NaCl in tap water which has been buffered by the addition of 5 to 10 per cent of a phosphate solution and adjusted to a final pH of 7 2

Cultures should be made by inoculating each tube of the medium selected with about 0 5 cc of the blood or urine of the patient The inoculated tubes should be kept in the incubator at a temperature of 28 to 30 C (82 4 to 86 F) and at the end of a week should be examined for the spirochetes by means of a darkfield microscope or stained smears They are usually numerous enough at this time to be demonstrated but sometimes spirochetes cannot be found until two or three weeks after inoculation of the cultures The urine contains the spirochetes from seven to ten days after the onset of the fever Dark field preparations or stained smears of the sediment should be examined If necessary a guinea pig should be inoculated with the sediment and cultures should be made if facilities are available

Agglutination tests have been devised for the diagnosis of infectious jaundice but these are most useful after the fever has subsided and as confirmatory evidence of a past infection since agglutinins persist in the blood for many months Either formalized cultures or living cultures may be utilized in these tests The agglutination titer is high from 1 500 to 1 15 000

The adhesion test of Brown and Davis (1927) has proved of practical value not only in the diagnosis of *L icterohaemorrhagiae* but also in differentiating it from other spirochetes The serum of the patient is added to a mixture of *L icterohaemorrhagiae* and either bacilli or blood platelets it is examined after a short time with the darkfield microscope The test is considered positive when the bacilli or platelets are found adherent to the spirochetes

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or four days About 20 cc should be administered at each injection The total dosage for an adult is from 40 to 60 cc daily for three or four days This method of treatment is of no value in severe infections if administered late in the disease The more promptly the antiserum is given the better the results

If it is impossible to secure the antiserum it has been found that the intramuscular injection of convalescent serum provided it has a high agglutinating titer (1 15 000 to 1 20 000) gives excellent results in treatment Injections of 30 cc should be given daily for three or more days depending on the response to treatment

General treatment is important Symptoms should be treated as they arise The bowels should be kept open and if necessary intravenous saline solution containing 5 per cent of glucose should be given If severe kidney symptoms develop intravenous injection of normal saline solution will be found to be beneficial The patient should not be allowed to leave his bed until convalescence is established The diet during acute symptoms should be liquid If vomiting is severe nutriment should be administered rectally or else glucose *should be given intravenously*

Mild cases require no special treatment but the patient should be confined to bed and carefully watched because severe symptoms may develop at any time During convalescence the diet should be nutritious Iron and arsenic may be administered for their tonic effect

PROPHYLAXIS

The most important phase of prophylaxis is the destruction of rats and the prevention of their breeding for rats are the natural reservoir of this disease (page 274) Rat bites should be cauterized and all necessary steps should be taken to prevent these rodents from coming into contact with food or drink Bathing or swimming in pools or streams known to be infected should be prohibited Since the spirochete has been found in the slime of mines and sewers and since it is the belief that infection occurs through abrasions of the skin miners or others coming into contact with the slime in mine passages should see that their skin is free from abrasions and if such are present should cleanse and disinfect the abrasions after such contact The same precautions should be taken by sewer workers since *L icterohaemorrhagiae* has been found in the slime of sewers The urine of patients suffering from infectious jaundice should be carefully disinfected because the spirochetes are frequently present in large numbers in the urine during and after convalescence The hands should be carefully sterilized after handling the urine of patients or after touching the soil of regions that are known to be infected If abrasions are present on the hands rubber gloves should be worn before such material is handled

It has been found possible to immunize animals by the injection of killed cultures of *L icterohaemorrhagiae* A vaccine prepared from killed cultures should prove of value in prophylaxis and should be tried if possible in the case of workers in mines and sewers where the infection is known to exist

indefinitely It is found in the blood in very small numbers during the febrile attacks and is difficult to demonstrate even in thick blood films or with the darkfield illumination Inoculation of white mice rats guinea pigs and

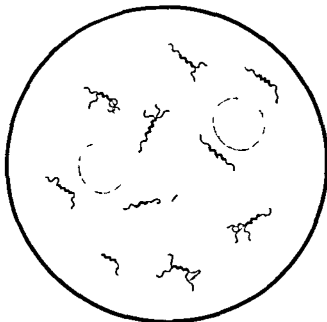


Fig 38 *Spirillum minus* the causative organism of rat bite fever Blood smear preparation stained to show flagella The round bodies are red blood corpuscles × 2 (After Wenyon)

monkeys with the blood is followed by infection white mice being the most susceptible In experimental animals the spirilla appear in the blood stream about seven days after inoculation and are found during the first two weeks of the infection and afterward in the connective tissues especially in the tissues of the lips and tongue Futaki and his colleagues who found the organism in man in the tissues near the site of the rat bite and in the regional lymph glands produced the disease in white rats guinea pigs and monkeys Experimentally infected animals usually survive the infection

Rat bite fever is transmitted to man by the bite of infected rats However the bites of infected cats mice dogs squirrels weasels and ferrets are also infective and have caused the disease in man Some authorities assert that the scratches of such infected animals are sufficient to transmit the infection It has been shown by surveys that about 3 per cent of the house rats in Japan are infected and that in that country the field vole *Microtus montebelloi* also transmits the disease to man

It is a curious fact that although infected rats transmit the disease to man by means of their bite the organism cannot be demonstrated in their saliva

CHAPTER XX

RAT-BITE FEVER

CHARLES FRANKLIN CRAIG

RAT-BITE FEVER [SODOKU SODOSHA (JAPANESE) CAT-BITE fever] is an acute infectious febrile disease caused by *Spirillum minus* It has an incubation period of variable length and is characterized by a sudden onset a peculiar eruption a relapsing fever lymphangitis and local enlargement of the lymphatic glands It is transmitted to man through the bite of infected rats With each access of fever the site of the bite becomes swollen and inflamed

HISTORICAL NOTE

Robertson (1931) stated that rat bite fever was first described by Wilcox and Watson in America in 1840 but nothing was known about its etiology until the researches of Futaki Takaki Taniguchi and Osumi demonstrated that it was caused by a spirillum which they called *Spirochaeta morsus muris* The work of Zuelzer (1921) Robertson (19 4) and others has shown that the causative organism is really a spirillum and that it is identical with one described by Carter (1888) in rats in India which he called *Spirillum minor* The name was afterward corrected to *Spirillum minus* which is the proper name of the organism

ETIOLOGY AND EPIDEMIOLOGY

S minus varies much in morphology It is usually a short rather stout spirillum showing only two spirals and measuring from 1 5 to 6 microns in length The longer forms show as many as eight or ten spirals The organism has pointed ends at each of which it has one or more flagella In the living condition it moves about rapidly by means of the flagella its movement being that of a vibrio This spirillum can be distinguished from the spirochetes by the fact that during propulsion its body remains motionless whereas the body of the spirochete bends

S minus (Fig 38) can be stained with the Giemsa or Wright stain but the best results are obtained with the Fontana or silver stains It can be cultivated upon the Noguchi medium (page 280) and subcultures can be maintained

indefinitely It is found in the blood in very small numbers during the febrile attacks and is difficult to demonstrate even in thick blood films or with the darkfield illumination Inoculation of white mice rats guinea pigs and

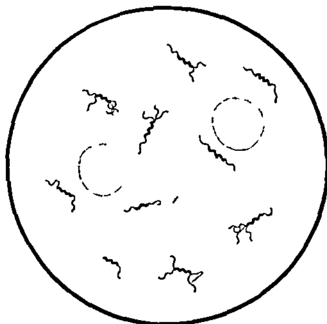


Fig 38 *Spirillu n n* the causative orgni m of rat l te fever Bl od smear preparation stained to show flagella The round bod es are red l l od rpuscles × 2 00 (After Wei yon)

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It is a curious fact that although infected rats transmit the disease to man by means of their bite the organism cannot be demonstrated in their saliva

unless the rats have lesions in the mediastinal glands lungs or bronchi in which case the spirilla may be demonstrated on rare occasions in the secretions It is thought that infection is usually caused by spirilla from the tissues of the rats lips or mouth which may be lacerated during the act of biting and in which the spirilla may be demonstrated Mooser (1925) and McDermott (1928) found that the eyes of infected rats are markedly inflamed and that the increased lachrimal secretion contains the spirillum Theiler (19 6) and Schockaert (1928) have produced the disease in man by inoculation with *S minus* that has been obtained from human patients and from infected rats One attack of the disease confers a lasting immunity not only to this spirillum but also to *other spirilla which have been isolated in various animals* The fact that rat bite fever patients are immune to infection from all these spirilla confirms the growing belief that this spirillum is identical with *Spirillum laverani* and *Spirillum muris* which are found in rats and mice in various localities

The *incidence* of rat bite fever is considerable in Japan but it is a rare infection in other countries As regards its *geographical distribution* in addition to Japan cases of the disease have been described in the United States Mexico Central America North and East Africa China Siam the Netherlands Indies and Australia

SYMPTOMATOLOGY

The *period of incubation* is uncertain the average period of incubation being from five to fifteen days up to sixty days following the bite of the infected rat The site of the bite heals before the appearance of symptoms The onset is sudden with a chill or chilly sensations severe headache anorexia and nausea rapid rise in temperature and marked prostration At the same time the scar of the bite becomes inflamed edematous and tender and the regional lymphatics and lymph glands also become enlarged inflamed and tender The muscles in the vicinity of the bite may be indurated the hands arms or legs may become edematous while vesicles may form in the scar tissue which may later become necrotic Nervous symptoms such as violent headache photophobia dizziness tinnitus aurium and localized areas of hyperesthesia or anesthesia may develop but such symptoms are not present in mild infections

In mild cases if fever is present it may not exceed 38 7 C (101 7 F) but in the usual infection the temperature rises rapidly to 39 4 or 40 C (103 to 104 F) reaching its maximum in about twenty four hours (Fig 39) It remains near this level for from three to six days when it falls by crisis accompanied by marked perspiration After a fever free interval of from three to ten days an exacerbation occurs accompanied by the symptoms noted in the primary attack *From two to as many as twelve such relapses may occur* covering several months in the most severe infections The symptoms become less severe with each relapse until either convalescence or death ensues

In most cases there is secondary anemia and during the acute attacks there is leukocytosis the polymorphonuclear leukocytes being increased during the

afebrile periods leukocytosis is absent but there is an increase in the mononuclear leukocytes and in the eosinophiles

The characteristic eruption of rat bite fever may occur during the initial

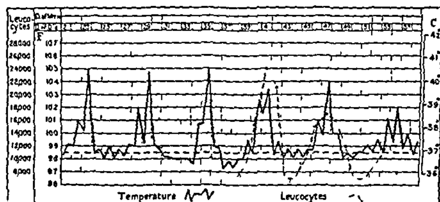


Fig 39 Temperature and leukocyte chart of a typical case of rat bite fever (After Tileston)

rise in temperature or during a relapse It is a maculopapular eruption appearing in irregular areas on the legs arms and trunk and is dusky red or purplish in color In mild cases no eruption may be noted and a hot bath is sometimes required to demonstrate it

With each relapse there is a recrudescence of local symptoms in the region of the bite but these gradually decrease in severity and finally disappear The site of the bite is marked by a more or less depressed purplish or dusky red scar varying in size with the severity of the local reaction

COMPLICATIONS AND SEQUELAE

Complications rarely occur in rat bite fever Bronchopneumonia bronchitis and enteritis have been observed septicemia and pyemia following infection of the local lesion caused by the bite which sometimes occur may prove fatal No sequelae of consequence have been reported

DIAGNOSIS

While the diagnosis of rat bite fever should rest upon the demonstration of the causative spirillum a clinical diagnosis is possible in moderately severe and severe cases The occurrence of a relapsing fever following the bite of a rat or other rodent after an incubation period of from one to six weeks accompanied by local inflammation of the healed lesion caused by the bite and by the characteristic eruption constitutes sufficient evidence upon which to base a diagnosis of rat bite fever Mild cases occur in which it is impossible to make a clinical diagnosis Laboratory tests must then be relied upon for diagnosis of the disease

LABORATORY DIAGNOSIS

S minus is found in such small numbers in the peripheral blood that dark field illumination or smears of the blood seldom show the organism nevertheless both methods should be employed Greater success in demonstrating the spirillum may be obtained by a darkfield examination of material obtained from the local lesion produced by the bite of serous fluid from a papule of the eruption or of material obtained by puncture of an enlarged gland Smears prepared from all such materials should be stained with the Wright Giemsa or Fontana stains before they are examined for the spirillum If all preparations are found negative a white mouse or rat should be inoculated subcutaneously or intraperitoneally with the patient s blood This should be obtained during a febrile period and if the infection is caused by *S minus* this organism will be found in the peripheral blood of the animal in from three to fifteen days usually in from eight to ten days

If several paroxysms of the fever have occurred the blood will contain agglutinins for *S minus* For that reason an agglutination test will be of value in diagnosis

DIFFERENTIAL DIAGNOSIS

Rat bite fever must be differentiated from relapsing fevers malaria and certain *Streptothrix* infections The characteristic eruption together with the local symptoms connected with rat bite fever suffices to distinguish it from the *relapsing fevers* while the absence of *Plasmodia* in the blood differentiates it from the *malarial fevers* Schottmuller (1914) Blake (1916) and Tunnicliff (1916) have described fevers following rat bites which are caused by species of *Streptothrix* Schottmuller has isolated two species *Streptothrix muris ratti* and *Streptothrix taraxericapapi* from two cases of fever following the bite of a rat and a squirrel respectively Such infections can be differentiated from rat bite fever only by the demonstration of the *Streptothrix* concerned

PROGNOSIS

The mortality caused by this infection is about 10 per cent in Japan but the percentage of deaths is less in the patients observed in other countries

TREATMENT

Hata in 191• demonstrated that the arsphenamines act as specifics in the treatment of this disease One injection of from 0 3 to 0 6 gm of neoarsphenamine is usually sufficient to effect a cure although some authorities prefer to give two to three intravenous injections of neoarsphenamine the dose varying from 0 3 to 0 44 gm for each injection The injections should be given at the beginning of the febrile period or periods Bismuth compounds also have a very definite specific action and antimony preparations especially stibosan are also curative During convalescence iron and arsenic are indicated for their tonic action and blood building properties

PROPHYLAXIS

The prevention of rat bite fever involves the destruction of rats and of their breeding places The methods to be applied for this purpose are the same as those employed in the prevention of plague (page 522) The bite of the rodent should be cauterized at once and some authorities recommend a prophylactic intravenous injection of neoarsphenamine

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CHAPTER XXI

SEVEN-DAY FEVER

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SEVEN-DAY FEVER [NANUKAYAMI SAKUSKU FEVER SHUEKI (Japanese) harvest fever autumn fever] is an acute infectious febrile disease caused by *Leptospira hebdomadis* It is characterized by an uncertain incubation period sudden onset marked prostration severe headache pains in the back and legs general glandular enlargement and a peculiar remittent temperature curve The fever usually lasts about seven days

HISTORICAL NOTE

Seven day fever was first accurately described by the Japanese physicians Ido Ito and Wani in 1917–1918 who also described its cause a spirochete which they called *Leptospira hebdomadis* This spirochete is identical with *Leptospira autumnalis* which was described by Kitamura and Hara in 1918

ETIOLOGY AND EPIDEMIOLOGY

In 1917–1918 Ido Ito and Wani in investigating a disease known in Japan as Nanukayami found a spirochete in the blood and urine which they proved to be the cause of the disease and which they called *Leptospira hebdomadis* Morphologically this spirochete closely resembles that of Weil s disease *L icterohaemorrhagiae* but according to Noguchi it is slightly longer than the latter The organism is present in the blood usually in small numbers from the second to the seventh day of the fever and after the crisis For a *period of several weeks it is found in the urine of the convalescent* patient and during this time the patient is infective This spirochete can be distinguished from others by serologic reactions After the crisis of the fever the blood of patients contains specific antibodies These antibodies may be demonstrated by injecting the blood intraperitoneally into the abdomen of a guinea pig together with a culture of the spirochete A positive Pfeiffer reaction will take place *Patients recovering* from an attack of seven day fever are usually immune to further attacks

L hebdomadis can be cultivated upon the Noguchi and other suitable media and guinea pigs can *be infected by inoculation with cultures or with* the blood or urine of individuals suffering from the disease

Seven-day fever occurs in Japan during the months of September and October and is commonly called harvest fever by the Japanese It may be transmitted from man to man through the contamination of food or drink with the urine of the infected individual but more often it is transmitted through the bite of the field vole *Microtus montebelloi* or through contamination of food or drink with the urine of these animals *M montebelloi* is the natural host of *L hebdomadis* and about 3 per cent of these animals have been found to be infected Because the method of transmission is through the field vole the disease is almost entirely confined to laborers in the fields in the endemic regions although some cases occur in other places as a result of infection from man to man The fever is endemic only in areas in which the field vole is present The field vole is also one of the most active agents in the transmission of tsutsugamushi disease or Japanese river fever acting as the host of the mite that transmits the causative organism of that disease

The *geographical distribution* of seven day fever appears to be limited to Japan China India Arabia and the Netherlands East Indies while similar fevers have been reported from the Federated Malay States and Sumatra The *incidence* is high among the laborers in the fields in the endemic regions in Japan but great epidemics have not been reported even in the endemic regions

PATHOLOGY

The pathology of seven day fever is unknown for the disease never terminates in death of the patient The presence of albumin in the urine and the fact that the spirochete that causes the infection is excreted in the urine for several weeks following an attack indicate that some pathological changes must occur in the kidneys However complete healing of any such lesions takes place since chronic nephritis never follows the infection

SYMPTOMATOLOGY

The incubation period has not been accurately ascertained in man but it appears to be short The onset is sudden and the symptoms resemble those of dengue and infectious jaundice With the onset of the fever there is usually a slight chill or chilly sensation Fever rises rapidly to 39 4 C (103 F) and is accompanied by aching in the muscles of the back and legs nausea anorexia headache and prostration After the initial rise in temperature the fever continues in a remittent fashion for seven days at the end of which it terminates by crisis when convalescence begins Fever seldom exceeds 40 C (104 F) and relapses do not occur A saddle back type of fever is reported as common

During the first three or four days of the fever there is marked leukocytosis in some cases but usually the leukocytes are only slightly increased The face is much flushed the conjunctivae congested and on rare occasions slight jaundice may develop toward the end of the attack There is marked hyperesthesia of the skin the muscles are tender on pressure and there is general enlargement of the lymphatic glands The eyes are brilliant and the general expression is of anxiety Marked mental depression may be present In rare

instances an eruption resembling that of measles has been reported on the forearms but such cases may have been dengue fever rather than seven-day fever A saddle back type of temperature curve has also been described in this infection but in all probability such patients were really suffering from dengue as the temperature curve in seven-day fever is remittent after the initial rise Mild cases occur in which the temperature returns to normal within two or three days but most patients have a fever for approximately seven days. Convalescence is rapid and uneventful although mental depression may persist for several days

COMPLICATIONS AND SEQUELAE

Complications and sequelae are apparently not present in this disease

DIAGNOSIS

Clinically it is often impossible to diagnose seven-day fever by the symptoms present especially in the milder infections which may be so mild as to be un recognized The occurrence in the endemic regions of a fever with sudden onset, accompanied by the classic symptoms is sufficient evidence upon which to base a tentative diagnosis but a positive diagnosis of seven-day fever cannot be made unless the causative spirochete is demonstrated in the blood or urine or in guinea pigs inoculated with infected blood or urine

LABORATORY DIAGNOSIS

During the febrile period of the infection *L hebdomadis* may be demon strated with the darkfield microscope in the blood or in blood smears stained with the Wright Fontana or Giemsa stains As the spirochetes occur in small numbers a prolonged search is often necessary in order to demonstrate them If the blood is negative guinea pigs may be inoculated intraperitoneally with from 3 to 5 cc of the patient s blood Infection of the guinea pig invariably follows if *L hebdomadis* is present Cultures of the blood or urine may be made upon the Noguchi medium (page 280) a diagnostic measure that is sometimes useful

After the termination of the fever the spirochete may be demonstrated in the urine by centrifuging and examining the sediment with the darkfield microscope or in blood smears If guinea pigs are inoculated the spirochetes will develop in the blood urine and viscera of the infected animals

DIFFERENTIAL DIAGNOSIS

Seven-day fever must be differentiated from dengue Weil s disease (infectious jaundice) relapsing fever and rat bite fever The differentiation from dengue is often difficult and in many mild cases of the latter disease it is clinically impossible Usually the more severe muscular pains postorbital tenderness saddle back type of temperature marked leukopenia and the characteristic eruption of dengue should serve to distinguish it from seven day fever Weil s disease or infectious jaundice is marked by the longer duration of the fever and the occurrence of jaundice which is usually absent in seven day fever In Weil s disease inoculations of guinea pigs with infected b[illegible] followed

by hemorrhages and marked jaundice in 99 per cent and by the death of all of the inoculated animals On the other hand in seven day fever the inoculation of guinea pigs is followed by general glandular enlargement jaundice in 17 per cent but the animals do not develop hemorrhages and the death rate is approximately 40 per cent The relapses which are a prominent symptom in relapsing fever are not characteristic of seven day fever Rat bite fever is distinguished by relapses and the appearance of a characteristic eruption

Modern research tends to suggest that *L hebdomadis* may be simply a variant of *L icterohaemorrhagiae* but this has not been proved

PROGNOSIS

The prognosis of seven-day fever is always excellent

TREATMENT

There is no specific treatment for seven day fever Usually little treatment is necessary beyond making the patient as comfortable as possible The administration of acetylsalicylic acid in doses of 0 325 gm (5 grains) every three hours will relieve the muscular aching and pains The bowels should be opened with a saline cathartic The diet should be light during the febrile period Usually anorexia is present but the patient should not be urged to eat until he desires to do so as the disease is of short duration so that abstinence from food is not harmful Some authorities have suggested the administration of the arsphenamines but it is believed that the harmlessness and short duration of the infection do not justify their administration

PROPHYLAXIS

The prophylaxis of seven-day fever consists in the protection of food or drink from contamination by the urine of patients in protection from field voles which carry the infection and in avoidance of known endemic areas The wound caused by the bite of the field vole should be cauterized with carbolic acid or with a strong iodine solution As some observers believe that handling the soil in regions infested with the voles may convey the disease through the spirochetes penetrating the skin such handling should be avoided

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CHAPTER XXII

PINTA

HOWARD FOX

THE WORD PINTA IS DERIVED FROM THE SPANISH PINTAR (to paint) or pinta (a spot) Pinta [mal del pinto (Mexico) carate (Colombia) cute (Venezuela) catiri (Honduras)] is an infectious disease caused by a spirochete which is identical in appearance with those of syphilis and yaws It has no relationship whatever to fungi The manifestations of pinta may be divided into primary secondary and tertiary stages The primary and secondary lesions vary greatly in appearance the latter simulating eruptions of psoriasis ringworm syphilis and the like After a year or more the late stage appears it consists of pigmentary changes which may last for an indefinite period The clinical appearance of the pigmentary (or dyschromic) stage is often characteristic and does not simulate any other known disease The Wassermann reaction in the dyschromic stage is positive in nearly 100 per cent of cases and the disease is amenable to treatment with antisyphilitic remedies

HISTORICAL NOTE

In 1898 Montoya y Flores made a mycologic study of carate (pinta) in Colombia ascribing the cause of different types of the disease to different fungi which he had cultivated from the cutaneous lesions These included especially *Aspergillus* and *Penicillium* which are ordinarily thought to be harmless saprophytes The work of this author was quoted in textbooks for forty years until the causative spirochete was discovered and his theories discarded The mycotic theory however continued to be held tenaciously by most writers even a dozen years after Menck (1927) had made the first important discovery in this disease He found that the Wassermann reaction of the blood was positive in nearly 75 per cent of a series of cases of carate examined at the hospital of the United Fruit Company in Santa Marta

After a study of the disease in both Colombia and Mexico I agreed with Gonzales Herrejon that pinta was certainly not a fungous infection but was probably a spirochetosis This was ten years before the causative organism was discovered *Before this discovery there were sound reasons for not accepting the*

fungous origin of pinta No one had succeeded in producing the disease in man or animals (with one doubtful exception) from cultures obtained from lesions of pinta When a patient with pinta emigrated to a region where the disease did not exist his lesions remained but it became impossible to cultivate the same organisms from the skin Finally the known fact that in rare cases the disease could be strictly limited to one side of the body (hemipinto) practically ruled out a fungous infection When in addition it was found that the Wassermann reaction was positive in a large percentage of cases and that the disease yielded to antisyphilitic treatment there seemed to be no ground for retaining the fungous theory of origin

The work of Menck was confirmed the following year by Register who found an even higher incidence of positive reactions (80 per cent in a series of 207 cases) Finally in 1930 a Mexican commission under the leadership of Gonzales Herrejon found the incidence of the Wassermann reaction in a series of 130 cases to be 97 per cent To prove that these patients were not suffering from syphilis a serologic survey was made in the state of Guerrero of persons without clinical signs of pinta This showed an incidence of 15 per cent of positive reactions approximately that of syphilis in that locality

The second and most important discovery was that of Grau Triana and Alfonso Armenteros who on August 3 1938 discovered the causative organism while working in the laboratory of Braulio Saenz in Havana Cuba Two days later similar organisms were found in cutaneous lesions of another patient by Pardo Castello This discovery was subsequently confirmed in Mexico and is now universally recognized

The third important discovery in pinta resulted from the researches of Leon y Blanco a Cuban and they have revolutionized our ideas of the early manifestations of pinta Physicians in Mexico had previously thought that the pigmentary disturbances constituted the only manifestations of the disease No attention was paid to certain eruptions which the natives called empeines and which they firmly believed were early lesions of pinta The proof that these early lesions or empeines were an essential part of the disease could never have been proved before the discovery of the spirochete

For much of our knowledge of the early as well as the late manifestations of the disease we are indebted to the scientific work of Gonzales Herrejon and Fernando Latapi in Mexico

ETIOLOGY

The spirochete discovered in 1938 has been proved beyond any doubt to be the causative organism of pinta It is morphologically indistinguishable from the spirochetes which cause syphilis and yaws It has an average length of 17 microns according to Leon y Blanco and has fine pointed ends without demonstrable flagella The organism is best shown under darkfield illumination but it can also be demonstrated in smear preparations stained with Giemsa stain and in tissues impregnated with silver nitrate In the tissues it is numerous between the cells of the rete and in the hair follicles and ducts of the seba

ceous glands Leon y Blanco has also found the organism in sweat overlaying affected areas

The organism has been found with great ease in all manifestations of the disease including the late pigmentary changes with the exception of the atrophic vitiligoid areas To demonstrate the spirochete one has merely to scrape the affected area superficially until a drop of lymph exudes

There is a difference of opinion about the possibility of culturing the organisms and of inoculating animals Curbelo and his associates state that they have cultivated the organism anaerobically and Saenz maintains that he has produced both keratitis and epididymitis in rabbits However both the Venezuelan commission and Leon y Blanco failed in attempts at cultivation and inoculation in animals

Various names have been suggested for the causative organism Brumpt called it *Treponema carateum* Leon y Blanco suggested that it be called *Treponema herrejoni* in honor of Gonzales Herrejon who has done so much to increase the knowledge of the disease The term *Treponema pictor* was suggested by Pardo Castello and *Treponema americanum* by Briceno Rossi A suitable name would be *Treponema* (or *Spirochaeta*) *pintae*

EPIDEMIOLOGY

Pinta is apparently confined chiefly to tropical or subtropical parts of the Western Hemisphere where the mean temperature is about 80 F It occurs especially in moist regions along river valleys It is not contagious and is apparently not conveyed through the placenta There are no cases on record of the disease occurring at birth

Pinta may appear at any age but most cases are observed in adults In the elaborate survey made in the southern half of Mexico from 19 9 to 1931 under the leadership of Gonzales Uruena statistics of 270 685 cases were given The greatest incidence of the disease was found in adults between the ages of forty and fifty It is probable that pinta is rare in the first year or two of life As the Mexican survey was made prior to the work of Leon y Blanco it was impossible to determine the exact duration of the disease in any case Many of the adults whom I saw had suffered for years from the late dyschromic stage In one extensive vitiligoid case there was still some evidence of activity (blue areas) in an eruption of twenty five years duration In another case the disease had been present for forty two years It seems probable that the infection is contracted most often in childhood or in adolescence

This disease occurs in both sexes and affects mainly the dark skinned races Indians Negroes and those of mixed blood It is decidedly rare in the white race in general though Pardo Castello states that 12 per cent of his cases in Cuba occurred in white persons

Geographical Distribution Mexico and Colombia furnish the largest number of cases of pinta Iriarte estimated that there were 400 000 cases in Colombia A careful survey made by Gonzales Uruena in Mexico disclosed the presence of more than 270 000 cases in the southern half of that country constituting about 11 per cent of two and a half million persons The is also

endemic but to a much less extent in Central America Venezuela Peru Ecuador Argentina and some of the islands of the West Indies including Cuba Haiti the Dominican Republic Guadalupe and the Virgin Islands There seems to be doubt about the occurrence of pinta in Brazil Souza Araujo stated in 1910 that it had not been observed in that country

Transmission The method of transmission of pinta is not definitely known but it seems probable that it is effected by direct contact with an infected person It has been shown that infection can be produced by inoculation of superficial abrasions of the skin Leon y Blanco found spirochetes in plantar keratoses in 9 of 11 cases This might well serve as a source of infection through any abraded surface of the skin of another person

No vector has yet been discovered though it is possible (as in yaws) for certain flies to transmit the disease mechanically The rarity of the disease in white persons argues against transmission by a vector and in favor of trans mission by contact The greater attention paid to personal hygiene by the white race suggests a cause for their comparative freedom

HUMAN INOCULATIONS

Leon y Blanco inoculated 28 volunteers including himself in Mexico and later inoculated 4 others in Cuba The procedure consisted of depositing the infected lymph on a superficial scarification of the skin Of the Mexican vol unteers 14 were normal persons 3 were syphilitic with positive serologic re actions 5 had pinta with secondary manifestations (so called pintides) and 5 were suffering from late (dyschromic) manifestations

Of the 14 normal persons 11 were inoculated in scarified areas and devel oped the disease In the 3 other normal persons the infected lymph was placed on normal skin with negative results though these volunteers were later in fected by inoculating scarified areas This proved conclusively that pinta could be transmitted from one person to another by inoculation

The 3 patients suffering from latent syphilis who were successfully inocu lated developed an initial lesion followed later by a somewhat typical sec ondary manifestation of pinta This apparently proved that pinta and syphilis are different diseases and that syphilis does not confer immunity to pinta

Three patients who had recovered from pinta showed initial lesions after inoculation but no secondary manifestations Five patients in the late dys chromic stage failed to show any primary lesions on the forty ninth day after inoculation This apparently proved that superinfection is possible in the early stage of pinta but that it does not occur in the late or dyschromic stage of this disease

Experiments of Leon y Blanco upon patients in Cuba proved that mal del pinto in Mexico and pinta in Cuba are the same disease

HISTOPATHOLOGY

The histologic changes in both primary and secondary lesions are similar in general The epidermis shows hyperkeratosis acanthosis intercellular edema and lymphocytic infiltration The cutis shows a dense infiltration of lympho-

cytes and plasma cells with a few polymorphonuclear leukocytes and histiocytes The infiltration tends to be perivascular and to surround hair follicles and sweat glands The endothelial lining of blood vessels may be invaded by the infiltration Even in this early stage the disturbance in pigmentation is noted by the presence of large numbers of melanophores in the cutis

The histologic changes in the late dyschromic stage have been studied by numerous investigators In my sections from cases of both blue and depigmented lesions it was found that changes common to both types were vacuoles in the rete absence of elastic tissue in the papillary and subpapillary regions and pigmentary dystrophy In brief the process was a mild inflammation leading to vacuolization in the epidermis slight edema in the papillae and subjacent levels disturbance of pigmentation and elastic tissue In the cases of blue pinta the presence of enormous numbers of melanophores was striking In the vitiligoid areas there was distinct atrophy of the epidermis with flattening or loss of the rete pegs and complete disappearance of pigment in both epidermis and cutis Even in these cases there was evidence of slight inflammation

SYMPTOMATOLOGY

Primary Stage The following description of the primary and secondary stages of pinta is taken from the writings of Blanco and of Latapie as I have seen no cases of pinta since these early manifestations were recognized In the experimental cases the period of incubation from the time of inoculation to the first appearance of the initial lesion varies from seven to ten days The lesion appears as a tiny papule which becomes red and elevated by the twentieth day Between the thirtieth and the fiftieth days the papule becomes an ill defined erythematosquamous plaque It gradually extends peripherally to form a patch 4 or 5 inches in diameter At the end of approximately five months this becomes surrounded by small macules or papules which fuse with it and may thus assume a circinate configuration Eventually it becomes impossible to distinguish the initial lesion from the secondary lesions Unlike the chancre of syphilis it never ulcerates In infections which are acquired naturally the initial lesions are said to occur on the uncovered parts notably the legs In the primary stage the Wassermann reaction is negative

Secondary Stage The secondary stage of the disease appears at the end of from five months to a year or more and shows the type of eruption called empeines by the natives of Mexico It consists of erythematosquamous patches which are in nowise characteristic as they may simulate psoriasis ringworm syphilis eczema or leprosy The scales may be branny and adherent or large and lamellar in type The color varies according to the color of the skin and the duration of the disease being pinkish at first and gradually becoming purplish or slate colored The lesions often show a circinate tendency The favorite sites are the extremities and the face (Fig 40) especially over the bony prominences In the secondary stage the Wassermann reaction is positive in 60 or more per cent of the cases

Although it has been proved that the disease may present an initial lesion followed by secondary manifestations it seems probable that in many cases these are inconspicuous or possibly absent Many patients with late pigmentary



Fig 40 Pinta Extensive eruption involving the face neck and trunk in a man of mixed Indian and Negro blood aged 5[illegible] The face showed diffuse bluish black pigmentation Other areas of complete depigmentation intermingled with numerous small areas of bluish pigmentation on normal skin produced an unusual mottled appearance Observed in Santa Marta Colombia

changes assert that they had never suffered from any previous eruption such as the empeines of mal del pinto

Late Dyschromic Stage Prior to the last three years the pigmentary changes of pinta were thought by all physicians to have been the sole manifestations of pinta These lesions show a characteristic picture unlike that of any other

disease of the skin The most striking feature at first glance consists of the vitiligoid areas (Fig 41) which often cause a piebald appearance and present a severe cosmetic defect



Fig 41 Pinta Generalized eruption of two years duration in a 5 year-old child Note vitiligoid areas surrounded by areolas of partial depigmentation Diffuse areas of blue pigmentation were also present on the face and other parts Observed in Iguala Mexico (Fox H Corpus Iconum Morborum Cutaneorum Nekam 1938)

The ordinary descriptions of the different colors of the lesions of pinta give a misleading conception One reads about red blue yellow purple black white pinta and one might expect to see a scarlet or crimson red a bright blue or a sulphur yellow for instance Actually there are only two striking colors —blue and white The white patches are those of complete depigmentation and cannot be distinguished from ordinary vitiligo The blue color is the characteristic one and is of a leaden or slaty hue The so-called red color which is rare appears as flushing of the skin such as would result if the patient had just stepped out of a hot bath The so called yellow pinta presents a dirty yellowish brown lesion and some observers do not think the term yellow should be applied to it

The leaden blue lesions of pinta occur as freckle like spots from a pinhead to a split pea in size or as diffuse areas of varying extent Areas of partial depigmentation often adjoin the vitiligoid ones indicating the transition from partial to complete loss of pigment A peculiar mottled eruption may occur on the flexor surfaces of the forearms due partly to partial depigmentation and partly to bluish or brownish hyperpigmentation

The favorite sites of the lesions are the uncovered parts of the body including the face and neck and especially the extremities The bony prominences are particularly affected including the malar regions nose chin lower part

of forehead knuckles knees and malleoli A characteristic picture is presented by triangular patches of complete depigmentation on the front of the wrist The palms soles and genitalia are usually spared The mucous membranes



Fig 42 Pinta Extensiv depigmentat on of twenty fi e years duration in ar I dian v om n 30 yea s old There we e also a few blue a eas on the face Observed in Mexico City

are not infrequently involved The pigmented hair of the body is not as a rule affected whereas there is an absence of downy hairs in the affected areas

A tendency to symmetry is often noted and at times the symmetry is striking *It was reported in 36 per cent of the cases in the Mexican survey made by* Gonzales Uruena In rare cases the disease may be strictly limited to one side of the body (hemipinto) as reported by Latapi

The amount of scaling in these late lesions is difficult to evaluate Scaling was noted in one third of the cases in the Mexican survey Much of the scaling may be due to lack of ablutions and some of it to parasitic infections In making direct microscopic preparations for fungus it is difficult to obtain enough

material by scraping as the skin of the affected blue areas is frequently devoid of scales

It is also difficult to judge the significance of itching Many patients had scratch marks especially on the legs some of which were certainly due to trauma and some to insect bites Pruritus observed in these late cases is not a prominent feature of the disease The same is said to be true of the early manifestations

The course of the late dyschromic (Fig 4) lesions is one of extreme chronicity when treatment is not given When the vitiligoid stage is reached the disfiguration is permanent

In this late stage of pinta the Wassermann and other serologic reactions of the blood are positive in almost 100 per cent of the cases pinta being similar in this respect to the secondary stages of syphilis and yaws As a rule the spinal fluid is normal

Some unexplained manifestations have been noted in cases observed in Cuba These were proved cases of pinta although many of them presented hyperkeratosis of the palms and soles as well as brownish macules in these regions Both Saenz and Pardo Castello reported such cases and it should be said that spirochetes were first demonstrated in a patient with plantar keratosis Saenz thinks that yaws and syphilis can be excluded by the absence of changes in the bones on roentgenologic examination In a considerable proportion of the Cuban cases of pinta changes were found in the spinal fluid including positive serologic reaction increased globulin and the syphilitic type of colloidal gold curve In some of the Cuban cases aortitis was observed and was thought to have a possible relationship to pinta These extraordinary differences from the Mexican cases deserve further study

In view of statements of Rodriguez Arjona that a type of pinta existed in Yucatan which consisted solely of vitiligoid patches (white pinta) I made a trip to Merida in 1937 to study this subject In a series of 5 patients the Wassermann reaction was uniformly negative except in 1 patient who had syphilitic infection of long standing As none of these patients showed blue lesions or other color changes of pinta except the white patches and gave no history of having had them the obvious conclusion was that they were simply suffering from vitiligo

COMPLICATIONS

With the exception of the cases observed in Cuba it would appear that there are no complications in pinta and that the disease constitutes solely a cosmetic defect There are apparently no constitutional symptoms that can be ascribed to the disease Patients suffering from pinta are able to work as hard as the average unaffected person

DIAGNOSIS

Diagnosis of the initial lesion and the secondary manifestations can only be made with certainty by finding the causative spirochete in the lymph ob

tained after scraping the affected area In the late dyschromic stage difficulty may arise when the blue patches have disappeared completely In the final stage of complete depigmentation clinical differentiation from vitiligo is impossible

PROGNOSIS

The prognosis is excellent as regards life with the possible exception of some of the Cuban cases in which changes in the spinal fluid and the aorta might conceivably affect the duration of life The prognosis is excellent as far as the cutaneous lesions are concerned if treatment is given in the early stage and also in the dyschromic stage before complete depigmentation has occurred Improvement cannot be effected as a rule in the vitiligoid areas

TREATMENT

The treatment of pinta is the same as that for the other spirochetoses yaws and syphilis that is by arsphenamine (or allied drugs) and bismuth All lesions except the vitiligoid ones disappear under treatment and leave no permanent trace Hyperkeratoses of the palms and soles are also said to respond favorably to treatment The effect of these drugs on the serologic reaction is less favorable In some cases the reaction becomes negative in others it remains positive even after long intensive treatment

PROPHYLAXIS

As the disease is probably carried directly from one person to another by close contact and as there is apparently no insect or other vector prevention of pinta apparently depends solely on personal hygiene

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CHAPTER XXIII

YAWS (FRAMBESIA TROPICA)

HOWARD FOX

YAWS [PIAN (FRENCH) FRAMBESIA (GERMAN AND ITALian) bubas (Brazil)] is an infectious disease caused by the *Spirochaeta pertenuis* It is confined strictly to the tropics and affects the Negro races almost exclusively It is acquired most often in childhood Like syphilis the manifestations may be divided into primary secondary and tertiary stages The common type of secondary eruption is characteristic whereas the tertiary (late destructive) lesions cannot be differentiated from those of syphilis Yaws is closely related to syphilis but shows enough difference to warrant its classification as a different disease It is a much less severe infection than syphilis and yields readily to treatment

HISTORICAL NOTE

The question of the origin of yaws is bound up with that of syphilis and has been a source of much speculation and difference of opinion The first description of what was apparently yaws (in the West Indies) was made by Oviedo in the sixteenth century It is thought by some however that the disease was first brought to America by African slaves The origin of yaws is an academic question that may never be settled

ETIOLOGY

Yaws is caused by the *Spirochaeta pertenuis* (*Treponema pertenue*) an organism which is morphologically identical with the *Spirochaeta pallida* It was discovered by Castellani in 1905 soon after the discovery of the spirochete of syphilis by Schaudinn and Hoffmann The organism is demonstrated by the same methods that are used for the *S pallida* It is easily obtained from the epidermal portion of the frambesiform lesions and has also been found in the lymphatic glands spleen and bone marrow It has not been demonstrated in the blood though monkeys have been successfully inoculated from the blood of persons suffering from yaws

Animal and Human Inoculations Experimental inoculations in rabbits and monkeys have not only served as diagnostic aids but have added much to the immunologic knowledge of yaws and syphilis Pearce and Brown obtained

a characteristic reaction by inoculating a strain of S *pertenuis* into rabbits testicles This reaction was described as a granular orchitis and according to these investigators was a practically constant feature of the infection and was unlike any lesion of the tunic observed in experimental syphilis in the rabbit There were furthermore no generalized lesions in other parts of the body such as are seen in experimental inoculations of rabbits with syphilis These results were confirmed by Turner who thought the reaction differentiated the two diseases Inoculation of the testes of the rabbit with S *pallida* produced a hard lesion which was unlike the reaction caused by the spirochete of yaws Of 97 rabbits inoculated by Turner with yaws only 1 showed generalized lesions as compared with 4° 2 per cent of the animals inoculated with syphilis From his experimental work with rabbits Reasoner concluded that yaws and syphilis were totally different diseases though he added it is very probable that they originated from a common stem

Inoculation of monkeys often causes an eruption which closely simulates that occurring in man as is shown in numerous illustrations published by Schobl *in the Philippine Journal of Science He considers that the* crucial diagnostic test for a doubtful lesion is the inoculation of a suitable animal

Immunity As a rule one attack of yaws is followed by permanent immunity Within the first three years however it is possible to produce a modified form of yaws by reinoculation but it is said that this becomes impossible at the end of ten years There is a striking cross immunity between yaws and syphilis An entire population such as that of Guam may be immune to syph ilis owing to the fact that all of the natives have been previously infected with yaws There are differences however between the immune state in the two diseases According to Schobl syphilis produces an immunity to itself sooner than it does to yaws and also sooner than yaws does to itself Schobl maintains that the cross immunity is not a proof of the identity of yaws and syphilis but on the contrary shows plainly that fundamental immunologic differences exist between the two diseases

Before the period of cross immunity is established it is possible for both man and susceptible animals to suffer from both diseases There are numerous cases on record of human beings who while presenting active lesions of one disease have acquired the other through natural or experimental infection

EPIDEMIOLOGY

Yaws is found only in tropical regions for in spite of its being transmitted it has never gained a foothold in the temperate zone It occurs most frequently in areas of low altitude and in some countries in rural districts as opposed to cities or towns where syphilis is more common The disease affects the Negro races almost exclusively and is two or three times as common in males as in females Yaws may be seen at any age though the infection occurs in the *great majority* of cases in childhood In a series of 1 800 cases in Jamaica Turner and Saunders found that the disease had been acquired before the age of fifteen in more than 90 per cent

Transmission Yaws is rarely if ever acquired by sexual intercourse probably due to the absence of mucous patches or other infectious lesions in the mucous membranes This constitutes a fundamental difference from syphilis in which nearly 95 per cent of infections are venereal in origin In Turner's statistics of 1 096 cases of yaws in Jamaica only 10 patients (less than 1 per cent) stated that the initial lesion (mother yaw) had been situated on the genitals All except 1 of these patients were below the age of puberty at the time of infection

It seems probable that yaws is often acquired by close personal contact just as impetigo contagiosa is transmitted from one child to another Ideal conditions for such a method of transmission are offered by the habits of primitive races in the tropics where the children wear little if any clothing and sleep together in crowded huts Although S *pertenuis* does not penetrate unbroken skin the native children are apt to suffer from open lesions resulting from such causes as traumatism or bites of insects

That flies may transmit the disease is also highly probable Kumm and Turner have shown that in Jamaica *Hippelates pallides* is a likely carrier of the infection They found swarms of these flies on lesions of yaws and observed more than 300 spirochetes in the diverticulum of a single fly It is thought that the flies transmit the infection by regurgitation on an abraded or ulcerated area It is possible for syphilis to be contracted in a similar manner by flies but instances of this mode of infection are exceedingly rare

Geographical Distribution Yaws has a wide distribution in the tropical parts of both the Old and the New World It is present in equatorial Africa the East Indies many islands of the Pacific (especially Samoa) in Malaya Burma Thailand the West Indies and parts of South America It is not common in India or China It has recently spread rapidly in Kenya Tanganyika and Uganda and according to Manson Bahr has disappeared to a great extent in Ceylon and Guiana where it was formerly extremely prevalent It is doubtful whether yaws was prevalent in the southern United States during the earlier days of slavery At present the disease is occasionally seen in the United States in emigrants from the West Indies or elsewhere

PATHOLOGY

Most of the histopathologic studies have been confined to the cutaneous lesions Comparatively little study has been made of the histologic structure of the initial lesion though Hallenberger and Stitt state that it resembles that of the secondary frambesiform lesions In contradistinction to syphilis which attacks all tissues especially those of mesodermal origin the pathologic changes due to yaws are seen mostly in the epidermis and in the later stages in the bones and joints In general it may be said that the cellular infiltration is largely composed of plasma cells and that it does not show the intimate relationship to blood vessels which is characteristic of syphilis Giant cells are rare and the infiltration is not divided into tubercles The epidermis is greatly thickened and as a rule it is only in this part of the skin that spirochetes can be found

The changes in the epidermis are those which are found in all proliferating infectious granulomas

The histologic structure of the late ulcerating lesions which are clinically indistinguishable from those of syphilis may also be difficult or impossible to differentiate They tend to show less of the endarteritis and thickening of the vessel walls which are characteristic of syphilis Herbert U Williams who studied the pathology of yaws and syphilis thought that differential diagnosis between the two diseases in the late stage was difficult or impossible

On the question of visceral involvement there is some difference of opinion Manson Bahr states that no visceral changes have been found peculiar to yaws Williams shares this view but thinks that evidence from autopsies is insufficient The question of involvement of the cardiovascular and central nervous systems will be considered later

SYMPTOMATOLOGY

There is an almost universal agreement that yaws is not acquired in utero The absence of intra uterine infection constitutes one of the striking differences between yaws and syphilis The common stigmas of congenital syphilis including Hutchinson s triad sabre tibia saddle nose and so forth are conspicuously absent in children whose parents suffer from yaws Powell who studied yaws in India observed 17 healthy babies whose mothers suffered from yaws during pregnancy The babies remained free from the disease

The almost complete absence of lesions of the mucous membrane in the early stage of yaws is another striking difference from syphilis There are no mucous patches of the vagina or other mucous membranes which as aforementioned probably accounts for the absence of venereal infections In rare cases lesions may occur on the lips or other mucous surfaces but as *Stannus* says such lesions do not represent part of the yaws efflorescence but are produced by spread or inoculation In the late stages of the disease the mucous membranes may be the seat of ulcerating destructive gummas which are clinically indistinguishable from those due to syphilis

The period of incubation is more difficult to estimate than in syphilis but it is generally thought to be three or four weeks During this period there may be mild constitutional symptoms consisting of nocturnal headache pains in the joints and a mild rise of temperature These often disappear with the outbreak of the first lesions There may also be a moderate enlargement of the lymphatic glands in anatomic relationship with the site of infection

Cutaneous Manifestations The initial lesion (Fig 43) which is often called the Mother yaw or Maman pian is totally different from the small hard erosion or ulcer which characterizes at least the majority of *syphilitic chancres* The initial lesion of yaws is precisely similar to the other frambesiform lesions which appear subsequently except that it is almost invariably the largest one In some cases no initial lesion is observed After full development to the size of a horse chestnut or even in some cases to that of a small apple the initial lesion remains for from two to four months or at times a year The

favorite site of the mother yaw is the lower part of the leg It is rarely seen on the scalp and occurred on the genitals in only 1 per cent of the large series of cases observed by Moss and Bigelow in Santo Domingo Eventually the



Fig 45 Yaws Initial lesion on a favorite site in a child three years of age Observed in Haiti (Fox H Archives of Dermatology and Syphilology)

initial lesion disappears spontaneously leaving only a slight amount of atrophic scarring

The secondary stage which represents a general dissemination of the spirochetes appears as a rule within six weeks to three months after infection Again this may be accompanied by constitutional symptoms which like those of early syphilis are usually mild The common type of eruption begins as small papules which some authors have called polypapillomas Some of these disappear without further enlargement while others show a tendency to coalesce soften and become crusted and form the typical frambesiform lesions The name frambesiform or raspberry like was originally given to the lesion as a whole It would seem however that a much greater resemblance to a raspberry is presented by the raw granular surface of the rete mucosum after removal of the crust The appearance of the frambesiform lesions runs so true to form as to merit the term monotonous The crusts are often amber

colored and suggest those of impetigo They do not resemble the pustular syphilide The duration of the frambesiform eruption varies from a few months to two or even three years the lesions appearing in crops in the cases of long



FIG 44 Yaws Profuse eruption of frambesiform type The right eye is normal except for involvement of the skin of the lid Observed in Haiti (Fox H *Archives of Dermatology and Syphilology*)

duration The lesions eventually disappear spontaneously without leaving any permanent trace

The frambesiform eruption (Figs 44 and 45) may be profusely scattered over the face trunk and extremities In other cases it shows a tendency to be located about the nose and mouth and anogenital region The frambesiform eruption may also assume a circinate configuration often spoken of as ring worm yaws To the experienced observer it does not as Hasselmann says resemble the annular papular syphilide which is relatively common in Negroes At least it does not show the delicate unbroken rings with hyperpigmented centers such lesions usually occurring on the face especially about the nose and mouth

A lichenoid type of eruption is a somewhat unusual manifestation It consists of miliary papules grouped in small patches The eruption has been termed keratoid by Schobl Sellards and Lacy from its resemblance to keratosis



Fig 45 Yaws Frambesiform eruption on a favorite site Observed in Haiti (Fox H Archives of Dermatology and Syphilology)

pilaris It bears a closer resemblance to lichen scrofulosorum (Fig 46) It is apparently the type of scaly eruption described by some writers as the earliest generalized eruption of yaws

A hyperkeratotic eruption of the soles and occasionally of the palms is a fairly common and characteristic manifestation of yaws It is spoken of as the crab or crab yaws by the natives of the West Indies this term being used because it is said that the affected person walks like a crab The lesions consist of discrete hyperkeratoses which often become fissured and secondarily infected by pyogenic organisms They are usually bilateral and may be fairly symmetrical That these lesions are undoubtedly due to yaws is proved by their containing spirochetes and by their response to treatment with arsphenamine (or allied drugs) and bismuth Turner reported that 1 614 syphilitic Negroes in Baltimore showed no plantar hyperkeratoses whereas such lesions were found in 47 7 per cent of 591 patients in Jamaica who were suffering from yaws It might be argued that these lesions are due to going barefoot although

they are not seen in barefooted Negroes in our southern states who suffer from syphilis Plantar keratoses should be classed as late secondary manifestations When untreated these lesions may remain for years



FIG 46 Yaws Frambesiform eruption about the mouth and lichenoid eruption on the cheeks Observed in Haiti

A macular eruption (roseola) similar to that of syphilis is as a rule conspicuously absent in yaws Many experienced observers state that such a manifestation does not occur As an exception Schuffner stated that he had observed a macular eruption in 4 per cent of his cases The failure to observe this type of eruption in yaws cannot be ascribed entirely to the difficulty of its detection in dark skinned races The macular syphilide is frequently observed in Negroes without difficulty

The presence of itching in yaws has been unduly stressed especially as a feature for differentiating it from syphilis Itching of any great severity should usually be judged objectively by the presence of such symptoms as excoriations

secondary infection and thickening of the skin Even the papular syphilide in the Negro occasionally shows scratch marks though this disease in general is non pruritic. The same is true of yaws Itching is of little or no value in differentiating the two diseases

Neither iritis nor alopecia has ever been observed in yaws This is in striking contrast to syphilis especially in the Negro in whom iritis (or iridocyclitis) is common Zimmerman found it present in nearly 13 per cent of American Negroes though others have noted a lesser incidence It is however more common in Negroes than in the white race Alopecia which occurs in syphilis as either a diffuse or patchy (moth eaten) type is unknown in yaws

After the termination of the secondary stage (at the end of one or two years) the destructive tertiary lesions may appear This may happen within a short time or even before the complete disappearance of secondary lesions Yaws however tends to differ from syphilis by the lack of a more or less lengthy period of latency between the early and later manifestations The tertiary stage is characterized by destructive lesions of the skin mucous membranes bones and joints which cannot be differentiated clinically from those of syphilis An ulcerating gumma due to yaws is the counterpart of the same type of lesion occurring in syphilis

Central Nervous and Cardiovascular Systems The extent to which the central nervous system the cardiovascular system and viscera are involved is a question about which there are differences of opinion Examinations of the spinal fluid in yaws have however usually resulted in negative serologic reactions Heinemann in 19 8 from a wide experience in Sumatra stated that he had never seen a positive Wassermann reaction in the spinal fluid of patients suffering from yaws Hasselmann said that the reaction was always negative and similar results were obtained in 1938 by half a dozen investigators (quoted by Strong) Most experienced observers also consider tabes and paresis to be rare or nonexistent in yaws Slamet Sudibyo examined the spinal fluid of 123 syphilitic patients and of 101 suffering from yaws He concluded that there was no definite evidence of the development in yaws of lesions of the central nervous system which resembled either tabes dorsalis or paresis He found no abnormalities in the spinal fluid after the third year On the other hand Harper and Lambert in the Fiji Islands where syphilis is apparently unknown found numerous cases of paresis and were of the opinion that many of these patients had previously suffered from yaws Several other observers such as Pardo Castello who obtained a positive Kahn reaction in 6 of his series of 25 cases in Cuba have found changes in the spinal fluid

In regard to the occurrence of cardiovascular changes in yaws the majority consider that they are decidedly rare However in a series of 722 autopsies in Haiti Choisser found ten aneurysms in persons who were supposed to have suffered previously from yaws The evidence was obtained from the history and previous residence in rural districts where yaws abounds and syphilis is rare Williams however considers the evidence insufficient to prove that aneurysms of the aorta are due to yaws

Bones and Joints Even in the osseous system it is believed that certain distinctions between yaws and syphilis are possible Williams who has made an intensive study of syphilitic bones mentions the moth eaten appearance of the outer table of the skull in syphilis though this is not often seen at present He says there is no evidence that such changes occur in yaws Maul in the Philippines has found rarefying osteitis (osteoporosis) to be common in yaws. The tertiary manifestations include localized and diffuse areas of osteoperiostitis of the long bones especially the tibia ulna fingers and clavicle synovitis and tenosynovitis some of which may produce severe deformities Hackett quoted by Manson Bahr speaks of the so called boomerang leg which occurs in Australian aborigines among whom it is thought that syphilis does not exist It is considered a manifestation of yaws and consists of an anteroposterior curvature below the knee with an anterior convexity The destructive changes in the nasopharynx (gangosa) will be mentioned later

Serologic Reactions Yaws is one of the triad of spirochetoses which at some stage gives practically 100 per cent of positive reactions to complement fixation and flocculation tests The other two diseases in question are syphilis and pinta The high incidence of these reactions occurs in the early (secondary) stages of both yaws and syphilis whereas in pinta they do not occur until the late (dyschromic) stage is reached According to Baermann (quoted by Strong) the percentage of positive Wassermann reactions in clinically positive cases of yaws is from 80 to 100 per cent in treated cases 50 per cent and in latent cases from 35 to 40 per cent

SEQUELAE

There are three unusual diseases many cases of which are now considered to be sequelae or late manifestations of yaws These are gangosa goundou and juxta articular nodes

Gangosa is a destructive rhinopharyngitis which is thought to be a manifestation of yaws because it appears in regions where this disease is especially common Gangosa which occurs mostly in adults has been observed in the Island of Dominica (West Indies) where 60 cases in a population of 000 were observed It is also seen in Guam the Fiji Islands the Belgian Congo and parts of tropical Africa Gangosa is said to begin in the palate which it eventually destroys as well as the nasal septum and surrounding soft parts The usual description is that it has a funnel shape with the upper lip as its lower border The larynx is seldom affected but at times the eyes are involved and the lacrimal ducts Strong who failed to find the vascular changes of syphilis in one case which he studied histologically quotes Hallenberger s opinion that gangosa is due to yaws on account of the absence of syphilitic manifestations in the blood vessels The disease occurs in untreated ignorant or neglected persons and its treatment is unsatisfactory

Goundou is an exostosis of the face which is seen in parts of Africa South America and Jamaica The natives who suffered from this disease were spoken

of as "horned men" by MacAlister who first observed them in 1882. The arguments in favor of its being a manifestation of yaws are that it often occurs soon after the frambesiform eruption that the patients are immune to heavy inoculations with yaws and that tertiary manifestations of the disease may coexist. Goundou begins usually in the nasal process of the superior maxillary bone. It forms an oval tumor which projects downward and outward and which may attain the size of an orange. It obstructs vision because of its situation and may also destroy the eyes. The growth itself is insensitive and is covered by normal skin. The treatment is by surgical removal. Some authors who do not think that goundou is related to yaws mention its similarity to Paget's disease (osteitis deformans), leontiasis ossea or osteitis fibrosa. A similar disease has been observed in higher apes.

Juxta articular nodes have often been described as late manifestations of yaws though precisely similar lesions occur in syphilis among persons who have never been in the tropics. The lesions are hard insensitive subcutaneous masses which as their name implies are situated most often in the neighborhood of joints. The majority occur about the elbows and knees. The skin over them is movable at first but later it becomes attached to the deeper parts. The lesions are chronic and show no tendency to disappear spontaneously. They do not ulcerate or cause subjective symptoms. Spirochetes have been found both in nodes which were thought to be manifestations of yaws and in those of syphilitic origin. Strong states that there is nothing entirely pathognomonic about the lesions. In the nodes of syphilitic origin spoken of at times as chronic fibroid syphilomas the structure of a gumma with a large amount of fibrous tissue has been found. The lesions slowly respond to intensive antisyphilitic treatment or they may be removed surgically.

DIAGNOSIS

The clinical diagnosis of the common frambesiform type of yaws is easily made and is substantiated by the demonstration of spirochetes and the serologic reaction. In doubtful cases the diagnosis may be confirmed by inoculations in animals (rabbits and monkeys).

Yaws and syphilis are closely related diseases. The morphologic identity of the causative organisms the same serologic reactions the same response to treatment and the clinical identity of the late manifestations might appear to be strong evidence that yaws and syphilis are the same disease. However it should be pointed out that three of these four similarities exist between pinta and syphilis which are totally different diseases.

For many reasons it would seem logical to consider yaws and syphilis as different though closely allied diseases. The differences between yaws and syphilis are numerous. Yaws is a non venereal disease whereas syphilis is usually acquired by sexual intercourse. The mucous membranes are not involved in the early stage of yaws and intra uterine infection is unknown. Roseola which is the commonest eruption of syphilis is almost unknown in yaws. Fur

thermore there are striking differences in the appearance of the initial lesion and in the secondary eruptions The comparatively slight involvement of vital tissues and organs in yaws the histologic differences between the two diseases in the early stages and finally the results of experimental work with rabbits and monkeys all lead to the conclusion that yaws and syphilis are not the same disease

One of the most ardent advocates of the unity of yaws and syphilis is Admiral Butler who has written extensively on the subject He considers yaws as an exanthem like disease of the children of primitive people (Stone Age childhood) which through improvement in personal hygiene clothing and treatment has been modified and changed to a venereally acquired disease He thinks the problem should be studied from the historical standpoint The scientific approach by experimental inoculations of man and animals is however a better method of solving the problem than is historical research

PROGNOSIS

The prognosis of yaws is usually good as far as life is concerned It is immeasurably better than that of syphilis The disease is much milder than syphilis and yields correspondingly better to treatment Manson Bahr says that judging from the statistics collected by Nicholle the mortality must be very small indeed

TREATMENT

The treatment in brief is similar to that of syphilis by arsphenamine (and allied drugs) bismuth and iodides Mercury however does not appear to be of value in yaws Castellini thinks that its failure to influence the secondary manifestations constitutes a differential feature between yaws and syphilis The treatment of yaws in the early stages gives surprisingly good results three injections of neoarsphenamine often resulting in a complete cure In some of the tertiary cases prolonged treatment is necessary In the mass treatment of native population bismuth has often been used instead of neoarsphenamine to save expense Intramuscular injections of sulpharsphenamine have been used by some clinicians because of the simplicity of administration As in syphilis the iodides have been helpful in the late stages Acetarsone (stovarsol) has also been used orally but as Strong says the full course of treatment with stovarsol may be more expensive than the course of injections with neoarsphenamine The contraindications to the use of arsenical preparations in yaws are the same as in syphilis Needless to say the general health and nutrition of the patient should receive proper consideration

PROPHYLAXIS

Prophylaxis is a matter of personal hygiene All open sores or ulcers in un affected persons should be dressed to prevent infection by contact or by flies Infected persons should be treated promptly and segregated if possible

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SECTION FOUR

DISEASES CAUSED BY RICKETTSIAE

CHAPTER XXIV

INTRODUCTION

HENRY PINKERTON

THE NATURE OF THE PATHOGENIC RICKETTSIAE

THE PATHOGENIC *RICKETTSIAE* ARE BIOLOGICALLY OF great interest because they appear to occupy a position intermediate between the free living bacteria and the smaller filterable viruses For this reason it seems desirable to discuss briefly the interrelationships of these three groups of pathogenic agents so that the *Rickettsiae* can be given their proper orientation

Certain free living bacteria such as the colon bacillus are able to live and multiply in media containing simple carbon compounds ammonia and inorganic salts Others like the influenza bacillus require more complex media that contain relatively unstable products of protein decomposition which are found only in extracts of blood and animal tissues The reason for this difference is that organisms of the first group possess a complete system of anabolic and katabolic enzymes while organisms in the second group lack certain enzymes and therefore require food which has been to some extent predigested

When these organisms invade animal tissues they multiply in the intercellular fluids of the body and are practically never seen within cells except in so far as they may be engulfed by the defensive phagocytic cells of the body These organisms are cultivated with relative ease on bacteriologic media

Organisms with still more restricted enzyme systems but still cultivable on cell free media are typified by *Bacterium tularense* and *Bartonella bacilliformis* These organisms are grown with difficulty and only in media in which certain complex biochemical and physical conditions are artificially created In infected tissues they multiply extensively within cells but are also capable of multiplying in intercellular fluids containing suitable products of metabolic activity of living cells

Below this level we find a large and important group of pathogenic agents for which conditions suitable for multiplication are found only in the cytoplasm or nucleoplasm of living cells This group includes the pathogenic *Rickettsiae* and the filterable viruses In the case of the pathogenic *Rickettsiae*

colony like masses of organisms which are seen within infected cells are of diagnostic importance In the case of a few of the larger filterable viruses similar colony like masses of elementary bodies are seen intracellularly but in most of the filterable virus diseases we see only homogeneous intracellular structures the so called inclusion bodies which may or may not be agglomerated masses of individual units of the infective agent Thus *Rickettsiae* differ morphologically from many of the filterable viruses chiefly in the fact that they are definite discrete clearly visible organisms There is however evidence to indicate that *Rickettsiae* although as strictly dependent on intracellular conditions as the smaller viruses have a somewhat more complex *enzyme system and are able to maintain within the cells which they* infect a certain amount of independent metabolic activity It is an established fact that *Rickettsiae* grow best in cells in which metabolic activity is lowered while the smaller and more characteristic viruses grow best in actively metabolizing cells

We may define the pathogenic *Rickettsiae* as small gram negative bacterium like micro organisms which are obligate intracellular parasites and which are adapted to life in insect tissues A large number of nonpathogenic organisms have been described in insect tissues some of which are intracellular and some extracellular The pathogenic *Rickettsiae* are probably related to this large group being members which have accidentally developed pathogenic properties for mammals

The important practical point emerging from this brief summary of the biologic nature of *Rickettsiae* is that the problems of epidemiology pathology diagnosis prophylaxis and treatment are in general similar to those arising with the virus diseases In both cases we are dealing with pathogenic agents which cannot be cultured on bacteriologic media which may require the employment of specialized laboratory studies for accurate diagnosis and in which epidemiologic and prophylactic studies must frequently take into consideration the existence of insect vectors and intermediate mammalian hosts The problem of prophylactic vaccination in both virus and rickettsial diseases centers around the development of methods for obtaining a high concentration of the pathogenic agent in media containing living or surviving cells The sulfonamides are ineffective in the rickettsial diseases and in the great majority of the virus diseases

THE INTERRELATIONSHIPS OF THE RICKETTSIAL DISEASES

A striking feature of the pathogenic *Rickettsiae* is their tendency to undergo biologic modifications of a rather permanent nature as a result of residence in different insect vectors and in different intermediate mammalian hosts In this respect also they resemble the filterable viruses Careful studies have shown that in spite of the large number of names that have been applied to rickettsial diseases in various parts of the world there are only three main types the typhus group caused by *Rickettsia prowazeki* and transmitted by lice and fleas the spotted fever group caused by *Dermacentroxenus rickettsi* and transmitted

by ticks and the tsutsugamushi group caused by *Rickettsia tsutsugamushi* (*R orientalis* and *R nipponica*) and transmitted by mites These three organisms have been assigned to a family the RICKETTSIACEAE Two distinct immunologic varieties of typhus and two of spotted fever are recognized It is probable that detailed studies such as those carried out by Zinsser in typhus would disclose similar strain variations in tsutsugamushi and further strain variations in the spotted fever group Cross immunity in experimental animals exists between the members of each group but not between members of different groups

The etiologic agents of Australian and American Q fever although differing from other pathogenic *Rickettsiae* in that they multiply extracellularly under certain conditions are otherwise very closely related to the latter A description of these diseases will be given because they are of great interest from the clinical point of view and because of the probability that they may occur in regions where they have not been recognized Although the *Rickettsiae* of American Q fever have been found to reside in the tissues of ticks there is no cross immunity between this disease and spotted fever or typhus and it appears to differ widely from tsutsugamushi

Trench fever is probably caused by an extracellular rickettsia like organism inhabiting the intestinal tract of lice Strictly speaking this organism should probably not be included with the RICKETTSIACEAE but since the disease is usually classed with the rickettsial diseases it will be discussed briefly for the sake of completeness

CHAPTER XXV

TYPHUS FEVER

HENRY PINKERTON

TYPHUS FEVER (TABARDILLO, BRILL'S DISEASE, EPIDEMIC OR human typhus, endemic or murine typhus) is an acute exanthematic febrile disease of variable severity with an incubation period of from eight to twelve days and with a duration in typical cases of about fourteen days. It is caused by a small bacterium-like micro-organism, *Rickettsia prowazeki*, which develops as an obligate intracellular parasite within endothelial cells lining the capillaries of various organs. The disease is characterized by a sudden onset with severe headache, continuous high fever terminating rapidly by lysis, and a macular cutaneous eruption which may later become hemorrhagic and which involves the entire surface of the body with thé exception of the face, head, palms of the hands and soles of the feet. Other important characteristics are the variable severity of the disease in different epidemics as well as in sporadic cases and the associated variations in symptomatology. Two varieties are recognized: louse-borne (epidemic) human typhus and flea-borne (endemic) murine typhus.

HISTORICAL NOTE

Typhus fever in the severe epidemic form has been recognized as a clinical entity for about four hundred years, although the accurate diagnosis in sporadic cases and the differentiation of the latter from other rickettsial diseases have been made possible only by laboratory methods devised during the past twenty years. In European literature the use of the term "typhus abdominalis" for typhoid fever has often led to the confusion of this disease with true typhus (typhus exanthematica), although the two conditions are of course entirely unrelated. For several centuries typhus has been recognized as one of the most formidable and devastating of all epidemic diseases. The tendency of the disease to occur when masses of people are crowded together under unfavorable living conditions was also recognized by early students, and the recognition of this fact is reflected in the application to the disease of the terms "war fever," "camp fever," and "prison fever."

The solution of the epidemiology of typhus is an achievement of the twentieth century. In 1909 a step of tremendous importance was taken by Nicolle, Comte,

and Conseil These workers who conclusively established the fact that the disease was transmitted by lice were able to transfer the disease to monkeys and guinea pigs Methods for the control of the disease were now outlined The dictum that without lice there can be no typhus although later shown to be inaccurate was at least correct in so far as it applied to widespread epidemics involving millions of people

Ricketts and Wilder in 1910 first described the etiologic agent of the disease in smear preparations of the intestinal contents of infected lice Da Rocha Lima in 1916 confirmed and extended this observation noted the intracellular location of the organism and named it *Rickettsia prowazeki* in honor of Ricketts and von Prowazek both of whom died of typhus acquired in the course of their studies At about the same time several workers found morphologically similar organisms in lice which had not been infected with typhus but further study showed that these organisms were located extracellularly while the organisms acquired by lice after feeding on typhus patients were always intracellular in the intestinal lining cells The probable relationship of an extracellular rickettsia like organism of the louse to trench fever will be discussed later

The extensive outbreaks of typhus fever during and shortly after the war of 1914–1918 greatly stimulated interest in the further study of the disease For the first time in history attempts to eradicate the disease by delousing the population on a large scale were carried out successfully For some unknown reason the disease did not acquire a foothold on the western front in spite of heavy louse infestation and the great crowding that existed there Severe epidemics broke out among the German Austrian and Russian armies in Serbia in 1915 In 1918 1919 and 1920 Poland and Russia were severely attacked by the disease The estimated number of cases in 19 0 in Russia alone was 4 000 000

Wolbach Todd and Palfrey in 1919 carried out carefully controlled experiments in Poland which entirely confirmed under ideal conditions the etiologic relationship of *R prowazeki* to the disease

In 1926 a new chapter in our knowledge of typhus fever was begun by Maxcy who discovered that typhus was endemic in the southeastern part of the United States under conditions which precluded the possibility of louse transmission During the years 1931 to 1936 the reported incidence of the disease gradually increased perhaps largely as a result of the recognition of mild cases which had previously escaped diagnosis and in 1937 more than 2 000 cases were reported Maxcy s careful epidemiologic studies showed that cases of typhus were concentrated in cities and towns and often several cases occurred among the inhabitants of a single building His studies suggested to him the possibility that rats might act as a reservoir of the infection and that some ectoparasite of the rat might be the vector to man Dyer Rumreich and Badger in 1931 recovered the virus of typhus from wild rats in Baltimore and evidence that the rat flea was the vector was first furnished by Dyer Ceder Rumreich and Badger in the same year

During the past fifteen years much progress has been made in the study of the growth requirements of *R prowazeki* and although the organism still refuses to grow in cell free media various ingenious methods for obtaining it in high concentrations for purposes of vaccination have been devised

ETIOLOGY

The etiologic role of *R prowazeki* for which strong evidence was advanced by da Rocha Lima in 1916 was firmly established by the studies of Wolbach Todd and Palfrey published in 1922 and has since been further confirmed by the work of numerous investigators The most significant evidence of this relationship consists in (1) the constant presence of the organism in an intracellular location in the tissues of man and laboratory animals suffering from the disease and in the intestinal lining cells of lice previously free from organisms after they have fed naturally on typhus patients or after they have been injected *per anum* with infectious material from a variety of sources (2) the production of the characteristic lesions of typhus in guinea pigs injected with emulsions of the intestines of lice containing the organism and the non infectivity of the intestines of control lice free from organisms or containing only extracellular organisms (3) the cultivation of the organism within cells by various tissue culture methods and in membranes of developing chick embryos and the correlation of the presence of visible *Rickettsiae* in the cells of such media with infectivity for the guinea pig even when the *Rickettsiae* have been maintained in such artificial media for many months and (4) the fact that the incubation period of typhus experimentally produced in guinea pigs by the injection of such media is shortened to forty-eight hours when enormous numbers of *Rickettsiae* are present in cells and is lengthened to eighteen or twenty one days when only a few *Rickettsiae* are found after long search (Pinkerton and Hass) Considering the louse the tissue culture media or the developing chick embryo as the equivalent of cell free bacteriologic media we may say that Koch s laws have been fully satisfied

R prowazeki in its most characteristic form appears as a minute diplobacillus each unit of the diploid form averaging about 0 6 by 0 3 micron Apparent measurements of single organisms may vary from 1 2 by 0 3 micron to 1 6 by 0 3 micron owing to the fact that the space between the two members of the diploid formation may not be discernible Forms apparently considerably smaller than these dimensions and of a size which one would expect to pass through porcelain filters are frequently seen The organism is generally accepted as non filterable but its rapid loss of virulence under most conditions when freed from its host cells throws some doubt on past observations and it would not be surprising if a more suitable technique should show that it was filterable under certain conditions

Short chains are not uncommon and long chains ranging up to 40 microns in length often curved to conform to the contours of their host cells are occasionally seen These long chains appear commonly in recently infected cells in tissue culture and in lice but have not been seen in mammalian tissue

in vivo The chains often appear as solid threads but careful study shows that they are in reality composed of many diplobacilli of characteristic size joined end to end The spaces between the pairs are greater than the spaces between the individual units of the diploid forms

The organism is commonly described as exhibiting marked pleomorphism but this feature has probably been exaggerated In heavily infected cells the organisms appear as minute coccoid or diplococcoid structures often barely within the range of visibility This is believed to depend on nutritional factors and it is unlikely that anything comparable to a true life cycle exists

The statement often seen in the literature that the etiologic agent of typhus may appear in three forms a filterable form *R prowazeki* and *Bacillus proteus* is not supported by any valid experimental evidence whereas positive evidence against such a view has been obtained by various workers who have studied the organism in tissue culture and in other types of artificial media containing living tissue

R prowazeki stains poorly or not at all with most aniline dyes and is gram negative in the sense that organisms cannot be recognized when stained by the Gram method The organisms can be stained clearly both in smears and in paraffin sections by the Giemsa method If the organism is to be stained in sections fixation in Regaud s fluid is extremely important since it gives results far superior to those obtained with other methods of fixation In both smears and sections *Rickettsiae* may stain blue or deep purple The organisms have a strong tendency to stain faintly and the deeper stains are obtained only when conditions are ideal A highly satisfactory stain for the organism is the Machiavello modification of Castaneda s stain With practice the laboratory technician can stain the organisms bright red by this method so that they stand out in sharp contrast to the blue staining cytoplasm in which they lie This staining method although it has recently been used successfully to stain the elementary bodies of psittacosis in paraffin sections has not thus far been found successful for staining *Rickettsiae* in sections

Two distinct varieties of the organism are recognized *R prowazeki prowazeki* the etiologic agent of the classic epidemic human louse borne disease and *R prowazeki mooseri* the agent of the type of murine typhus discovered by Maxcy and later shown to be transmitted to man by the rat flea The variety name is in honor of Mooser who first saw the organism in enormous numbers in the scrotal sac of intraperitoneally injected guinea pigs

Morphologically these two varieties of typhus *Rickettsiae* are identical and complete cross immunity between them is found to obtain in guinea pigs The murine organism however produces a febrile disease in rats with many *Rickettsiae* in the exudate of the scrotal sac while the human strain produces only a nonapparent infection The murine organism injected into the louse (*Pediculus humanus*) *per anum* kills this arthropod in a few days whereas *R prowazeki prowazeki* requires about three weeks In male guinea pigs after intraperitoneal injection no grossly visible general peritonitis is seen with either strain With the murine strain however an acute inflammation of the

scrotal sac manifested externally by a red swollen scrotum (the Neill Mooser reaction) occurs almost constantly whereas with human strains such a reaction occurs rarely and is so mild when it does occur that it is usually overlooked. In murine strains smears from the exudate of the scrotal sac commonly show many serosal cells literally packed and distended with *Rickettsiae* (a phenomenon first noted by Mooser) In human strains this phenomenon can usually be brought to light with patience but is the exception rather than the rule

Zinsser demonstrated certain differences in the agglutinability of suspensions of the two types of *Rickettsiae* by specific antisera Agglutination takes place in higher titers when each strain is acted on by its own specific serum although cross agglutination is definitely seen and in fairly high titers The differences are similar to but rather less striking than those found for example between the *A* and *B* strains of the paratyphoid organism

Perhaps most important of all it has been found that for some unexplained reason human *Rickettsiae* multiply less freely than do murine *Rickettsiae* in tissue culture and under most other artificial conditions which have been employed to obtain *Rickettsiae* for the purpose of preparing vaccines This point will be discussed again The differences between the two strains are summarized in Table IV

EPIDEMIOLOGY AND GEOGRAPHICAL DISTRIBUTION

The importance of these relatively minor differences between the two recognized strains of typhus *Rickettsiae* lies in the fact that they suggest a permanent modification of one strain as a result of prolonged residence in a different species of mammal and in a different insect vector This fact must be taken into consideration in any attempt to work out accurately the epidemiology of the disease and also in any attempt to conquer the disease permanently by vaccination on a large scale Whether the human type is the original and the murine type the modification or vice versa is not yet clear Zinsser as a result of his intensive studies believed that the human type was antigenically the broader but recent observations have reopened this question

Murine typhus has been found in rats and sporadically in man in practically all parts of the world Human louse borne typhus has occurred in widespread epidemic form chiefly in certain regions in Europe but less extensive outbreaks have occurred in Asia Minor Asia Africa Syria Palestine and even in the United States The most important foci for the human type of typhus are in Russia Poland and Rumania

Human typhus is primarily a disease of temperate and cold countries and is rare in the tropics probably because conditions for the breeding of the human louse are less favorable in warm countries The incidence peak of murine typhus on the contrary is in the summer months

It is commonly assumed that a few cases of murine typhus occurring under suitable conditions of overcrowding and lousiness could in the course of months or years initiate an epidemic of the more severe type of louse borne infection This possibility has not however been proved and it is at least

Table IV

COMPARISON OF HUMAN AND MURINE STRAINS OF TYPHUS RICKETTSIAE

	H m S *R p owazek p otea k*	M r S AI *R prou sek moo*
Vector to man	Lous (*P d ul h m s*)	Rat flea (*Xe p yll che p s*)
Cl nical p cture n man	Char cterist cally mo seve e	Characte istically m ld
Outbreaks	R pon ble for most wide pread and se re ep demic	Us ally sporad c o endemic
React on n rats (nt aperito eal njection)	Non pparent infect on	Febrile d sease—exudate and *R k ttsiae* in rotal sac
React on n mal guinea p gs (intraperitoneal inject on)	Scrot l react on are mild and trans ent *Rickett s a* arely seen	Sc otal reaction con tant w th huge numbers of ckettsia filled cells
React on n li e (nject on per anum)	Lice die in about three weeks	Lice die in a few days
Agglut n t on	In h ghe d lut on by specific mmune serum	In h gher dilut on by specific immune ser m

theoretically possible that the two types of disease are so permanently modified that the change of one type into the other would require centuries rather than years

Zinsser in a study of sporadic cases of typhus in the North Atlantic states, found that most of these cases occurred in people who had migrated from Europe in the recent or remote past He recovered strains of the human type of the disease by injecting the blood of such cases into guinea pigs His studies strongly suggest that contrary to the view previously held the etiologic agent of human typhus may lie dormant in human beings for years and may cause late recrudescences of the disease Obviously this observation suggests that man may be a reservoir of the human form of typhus and may be responsible for its preservation during interepidemic periods without the previously hypothecated intervention of the rat and the rat flea

In any case it is clear that murine typhus transmitted from rat to man by the bite of the rat flea can never be a factor of great economic importance because the rat flea prefers to feed on rats and only attacks man when its more natural host becomes through death or otherwise unavailable The blood of human beings obstructs the intestinal tract of the rat flea and the consequent hunger causes the flea to bite man repeatedly However the rate of infection by this unnatural method is insignificant in comparison with the rate of infection attained by the more natural route of man louse man It is therefore obvious that the possibility of a devastating epidemic can exist only as a consequence of overcrowding and infestation with lice Given these two factors epidemic disease is almost certain to occur sooner or later whether such a catastrophe can originate from a single case of murine typhus or whether it requires a human strain for its initiation

The actual mechanism of transmission by the louse is probably by the entrance of louse feces, which contain many *Rickettsiae* into the wound produced by the bite The organisms are not found in the salivary gland of the louse and there is no evidence that they are directly injected into the skin of human beings

PATHOLOGY AND PATHOGENICITY FOR ANIMALS

Man monkeys guinea pigs and rats are susceptible to typhus although human strains produce only nonapparent infection in the latter animals Murine typhus *Rickettsiae* are also known to survive in the spermophile wild mouse cotton mouse and old field mouse for periods ranging up to several months A febrile disease is produced in the jackass by both strains of typhus

In those lower animals in which a febrile disease occurs the pathologic changes are in general identical with those observed in man The occurrence of the scrotal reaction in guinea pigs and rats in response to injection with the murine virus is dependent on an artificial route of inoculation (the intraperitoneal) and also on the anatomic continuity of the scrotal sac with the abdominal cavity and consequently does not occur in man Cutaneous reactions although they may occur are inconspicuous in the lower animals With

these exceptions the following description of the pathology in man can serve almost equally well for the pathology of the disease in the susceptible lower animals It should however also be noted that the focal brain lesions which are characteristic of the human strain of the disease in both man and lower animals are much less conspicuous in guinea pigs reacting to murine strains and practically do not occur with these strains in male guinea pigs in which a well marked scrotal reaction is seen

Gross pathologic changes are in general not impressive The macular skin lesions of the relatively early cases fade rapidly after death but petechial hemorrhagic lesions are commonly persistent Areas of gangrene on the skin resulting from occlusion of small blood vessels are occasionally seen The other gross changes seen are essentially those of any acute infectious disease and include slight enlargement of the spleen cloudy swelling of the viscera and occasionally non specific focal necrosis of the liver Bronchitis and bronchopneumonia are almost constant findings but they are complications of the disease and not strictly speaking a part of the general pathologic picture Thrombosis of the large blood vessels is occasionally found and the brain may show edema and congestion

Microscopically the essential pathologic change is seen to be a generalized proliferative endangiitis involving chiefly the arterioles precapillaries capillaries and venules but occasionally affecting the larger vessels These lesions are produced by the growth of *Rickettsiae* in the endothelial cells lining the vessels In capillaries swelling and proliferation of the infected endothelial cells often cause occlusion In larger vessels thrombosis is a result of damage to the endothelial cells The walls of the small blood vessels show some inflammatory reaction but this is less striking than in spotted fever and the most characteristic feature is the accumulation of mononuclear cells in such a way as to form small nodular lesions in the perivascular regions These typhus nodes are found in many organs but are most prominent in the skin and brain

The characteristic brain lesion as seen in sections consists of from ten to one hundred or more mononuclear cells some of which are neuroglia cells while others are phagocytic mononuclears of local origin with a variable but usually small number of neutrophiles These lesions on careful study are seen to center around small capillaries the endothelium of which shows proliferation

Similar changes in the skin but often involving larger vessels and accompanied by thromboses are of constant occurrence and here larger perivascular infiltrations are seen *Rickettsiae* may be demonstrated in the skin lesion more easily than in lesions of other organs and biopsy of the skin may be utilized as a diagnostic procedure The *Rickettsiae* are seen only in the endothelial cells lining the vessels in contrast to spotted fever *Rickettsiae* which are also present in smooth muscle cells of the vessel walls

The myocardium usually shows fusiform collections of inflammatory cells chiefly mononuclears between the muscle fibers This lesion like the brain lesion is dependent on damage to small capillaries

The bronchitis and bronchopneumonia that are frequently found post mortem in typhus fever are of the usual terminal type and do not differ from that seen in other diseases

SYMPTOMATOLOGY

The clinical picture of the human type of the disease as seen during epidemics is fairly constant and characteristic Mild *prodromal symptoms* consisting chiefly of a feeling of general malaise may be present for a day or two preceding the onset of actual illness but these symptoms are of no diagnostic importance and are usually absent

The true *onset* is remarkably abrupt and may be associated with actual collapse in the midst of physical work Severe frontal occipital or generalized headache almost invariably appears at the time of onset but disappears as a rule during the first week of the disease Transitory chills or a sensation of chilliness are associated with the onset in most cases Fever is usually present a few hours after the abrupt onset and sweating pain in the back and limbs vomiting and constipation are common in the early stages of the disease Anorexia during the first few days is the exception rather than the rule

Rash During epidemics a presumptive diagnosis may be made on the basis of this picture of the early symptomatology just described otherwise it cannot be made until the appearance of the rash usually sometime between the fourth and the eighth day of illness The early rash (Fig 47) is a pinkish macular eruption the individual lesions being rough oval or slightly irregular and ranging up to a maximum diameter of about 6 mm *It appears first* on the chest and upper abdomen the lesions are most numerous on the trunk extremities and neck but rarely involve the face Unlike the lesions of spotted fever the lesions of typhus almost never involve the scalp the palms of the hands or the soles of the feet These early macular lesions disappear on pressure and are rarely palpable In late stages the lesions may become hemorrhagic and palpable may be overlaid by a mottled erythema and may fail to fade on pressure The eruption persists until death or until defervescence when it rapidly disappears

Temperature Following the initial chill if this is present the temperature rises rapidly or by several successive steps to 39 5 C (103 1 F) 40 C (104 F) or rarely to 40 5 C (105 F) with partial remissions most often in the morning until the crisis when it falls suddenly (Fig 48) There may be one or more transient rises in temperature during the next two or three days but these are clinically unimportant and do not affect the general condition which is suddenly and markedly improved In certain cases in which the patients become comatose normal temperatures for several days preceding a fatal termination have been described The height of temperature is not always an accurate index of the severity of the infection and irregularities of the temperature curve are often seen

Pulse and Respiration The pulse is subject to daily variations ranging from 80 to 150 per minute these variations are at times correlated with the varia

tions in fever and at other times are more closely correlated with the mental symptoms In general the acceleration of the pulse rate is about proportional to the degree of fever Respirations are somewhat increased in uncomplicated cases and markedly increased when bronchopneumonia develops



Fig 47 Typhus fever showing the erythematous and petechial eruption in the second week of illness (Wolbach Todd and Palfrey The Etiology and Pathology of Typhus Harvard University Press)

Neurological Symptoms During the first week of the disease as the headache recedes the patient may show excitement tense anxious facies or may become delirious In other cases stupor is more prominent or there may be alternation of stupor and delirium These nervous symptoms tend to increase during the course of the illness but clear up rapidly with the fall in temperature in recovering cases In unfavorable cases coma may persist for several days before death Abnormalities in reflexes have not been described a fact which is rather remarkable in view of the cerebral changes which are similar to those seen in the virus encephalitides

Course of the Disease During the entire febrile course of the disease the patient s general condition becomes increasingly poor In uncomplicated cases death is probably caused by circulatory collapse As the disease progresses mental disturbances increase the skin becomes hot and dry and the patient complains of great thirst Incontinence of urine and feces may develop Coughing of sufficient severity to be troublesome is seen in about one half of the cases even in the absence of bronchopneumonia and a few moist râles may

Fig 48 Typhus fever (Wolbach Todd and Palfrey The Etiology and Path phus Harvard University Press)

be heard at the base of the lungs in most cases These clinical features are probably manifestations of pulmonary congestion There is complete loss of appetite and consequently the maintenance of nutrition becomes a difficult problem At the time of the crisis or termination of fever by rapid lysis which most often occurs on the fourteenth day all unfavorable symptoms are rapidly ameliorated if recovery is to take place The patient becomes rational appetite returns and although there is still danger of circulatory collapse for several days the entire clinical picture improves rapidly Convalescence in uncomplicated cases is usually uneventful and takes place in two or three weeks Fatal termination most often occurs between the twelfth and fourteenth days but may take place as early as the sixth day or as late as the twenty seventh day Exacerbations during convalescence have not been described and residual symptoms are exceptional In general the disease may be described as a self limited one

Late Recrudescence Until recently recovery from typhus was believed to be invariably accompanied by the disappearance of the etiologic agent from the body *and by the acquisition of long lasting immunity* The *observations of* Zinsser however indicate that *Rickettsiae* may persist in the body for years and that late recrudescence may occur It seems probable that this occurs chiefly after mild infections acquired in childhood and that recrudescences rarely follow a severe acute attack of the disease

The symptomatology of *the murine or flea borne form of the disease* is in general similar to that of human typhus but the course of the disease is usually much more benign and the fatality rate much lower Ambulatory cases have been described and the cerebral symptoms usually consist of irritability and apathy instead of the delirium and stupor which is so characteristic of the human type The chronological course of the disease resembles that of epidemic human typhus but the rash may be less extensive and atypical in form

COMPLICATIONS AND SEQUELAE

Stupor progressing to coma and resulting from extensive cerebral involvement is probably to be regarded as a characteristic of the disease rather than as a complication since the characteristic focal brain lesions are found in practically all fatal cases The commonest complication is bronchopneumonia This frequently occurs as a terminal event in comatose cases but may also occur during the course of a case of moderate severity Although extensive bronchopneumonia is much to be dreaded many cases with limited involvement of the lungs recover

Large localized areas of gangrene resulting from thrombosis of larger blood vessels occurred in about 3 per cent of the cases studied by Wolbach Todd and Palfrey Parotitis otitis media and erysipelas are complications of less frequency and importance It may be many weeks before the patient is able to resume his customary activity but this feature is no more striking than would be expected following recovery from any severe generalized infection There are no true *sequelae*

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

During epidemics individual cases are readily diagnosed on the basis of the *clinical picture* the most important features of which are the sudden onset with severe headache the temperature chart the rash of typical appearance and distribution and the mental symptoms The clinical pathologic findings other than the Weil Felix reaction are not specific There is usually mild to moderate albuminuria The leukocyte count varies from normal to 18 000 or 0 000 but is usually between 10 000 and 14 000 with or without the appearance of a few immature granulocytes The spinal fluid is usually negative but may contain from 50 to 100 lymphocytes

The Weil Felix reaction is of great diagnostic value and may even be helpful in distinguishing between typhus spotted fever and tsutsugamushi disease (The reactions are tabulated in the chapter on spotted fever (page 350) Agglutination with *B proteus* OX19 in dilutions of 1 100 or over furnishes important confirmatory evidence that the disease in question is typhus Agglutinins usually appear during the first week A rise in the titer of agglutination on successive tests is perhaps of greater importance than the actual height of the titer on any one examination Of 83 cases studied by the author in Poland in 1919 only 3 failed to give a positive reaction at 1 100 or over and 56 cases were positive at 1 800 or over In murine typhus the Weil Felix reaction is fully as characteristic as it is in human typhus The Weil Felix reaction is an example of non specific agglutination and is probably dependent on the fact that *Rickettsiae* and certain strains of *B proteus* have a common carbohydrate antigen as suggested by the studies of Castaneda

In the *differential diagnosis* of early cases before the appearance of the rash many infectious diseases such as influenza pneumonia encephalitis meningitis scarlet fever measles and generalized sepsis must be considered and ruled out as far as possible by appropriate diagnotic tests Typhoid fever may be ruled out by blood culture by the Widal reaction the leukopenia slow pulse and by the different appearance and distribution of the rash The rose spots of typhoid are less numerous than the typhus lesions (in their characteristic form)

I have recently seen several cases in which a generalized eruption from sulfanilamide administration closely simulated the rash of typhus or spotted fever In several other instances in which there was not a history of chemotherapy febrile exanthematic diseases have been carefully studied by all available means without arriving at a diagnosis

In mild sporadic cases with atypical cutaneous lesions differential diagnosis from spotted fever may be extremely difficult This problem is discussed in the chapter on spotted fever in which laboratory aids in diagnosis are considered in detail

PROGNOSIS

In general sporadic cases of murine typhus have a good prognosis the mortality rarely exceeding 1 or 2 per cent and fatalities occurring largely

among the aged In epidemics of louse borne human typhus the mortality ranges from 10 to 70 per cent and is much higher among foreigners than among native populations probably because many of the latter have had mild attacks in childhood The prognosis is much better in children for the reason that they appear to have better resistance During the course of the disease the general condition of the patient particularly with respect to mental symptoms is of greater importance than the temperature curve The prognosis is favorably influenced by intelligent supervision and careful nursing

TREATMENT

Treatment by convalescent serum has not given particularly encouraging results Serum obtained from a horse which had been immunized against murine typhus *Rickettsiae* gave somewhat encouraging results in the hands of Zinsser and others but this method of treatment is in the experimental stages In the absence of available specific measures the treatment should be supportive and symptomatic Topping has obtained negative and even suggestively detrimental results in the treatment of experimental typhus in guinea pigs with prontosil and sulfapyridine In the present state of our knowledge compounds of this type should not be given except in cases of late bacterial complications such as pneumonia Pinkerton and Bessey have shown that riboflavin deficiency leads to a striking and apparently specific loss of resistance to murine typhus in the rat and on theoretical grounds the injection of crystalline riboflavin in man might be of value particularly if the antecedent dietary history suggests a possible deficiency of this vitamin Other vitamins may be administered on general principles but are probably of less importance than the general state of nutrition A liquid and soft solid diet varied to suit the appetite of the patient should be given and liquid nourishment may be given to unconscious patients by tube The author has recently found that the withholding of food from the time of inoculation causes marked loss of resistance to experimental typhus in the guinea pig occasional animals dying with overwhelming infection on the third or fourth day after injection This observation still further emphasizes the importance of nutrition in typhus and suggests that it might be advisable to give concentrated amino-acid preparations such as Amigen by stomach tube

PROPHYLAXIS

Personal prophylaxis during epidemics of human typhus consists primarily in the avoidance of lice Louse proof gowns such as those described by Wolbach Todd and Palfrey should be worn by hospital personnel and patients should be carefully deloused on entering hospitals Prophylactic delousing of the general population on a large scale is of great importance and adequate control of this factor in interepidemic periods if this were possible would undoubtedly prevent the occurrence of important epidemics In the case of murine typhus the extermination of rats and avoidance of the possibility of being bitten by

rat fleas are likewise measures of obvious importance It should be remembered that the rat flea is particularly apt to bite man when its natural host, the rat, is killed

The principle of vaccination by formalinized or phenolized suspensions of *Rickettsiae* is based on sound experimental evidence that immunity of relatively long duration may be produced in this way Weigl in 1930 produced a fairly effective vaccine against human typhus from the intestines of lice infected by rectal injection This method was patterned after a similar method previously devised by Spencer and Parker for making vaccine against spotted fever from the tissues of infected ticks Weigl s method is not applicable to vaccination of man on a large scale Recently various other methods for obtaining high concentrations of *Rickettsiae* have been devised Reduction of the resistance of rats by x ray leading to extensive multiplication of *Rickettsiae* in the peritoneal lining cells is a method of great value in murine typhus but is not applicable to human strains For human strains the available methods in addition to the Weigl louse method are (1) the agar slant tissue culture method of Zinsser and his co-workers ( ) Castaneda s rat lung method and (3) the yolk sac method recently worked out by Cox The latter method is being used on a large scale for vaccination in the army Preliminary reports suggest that although it is not completely effective the incidence and mortality of typhus are significantly reduced by its use It is probable that more complete information on the practical value of the method will be available in the near future

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CHAPTER XXVI

SPOTTED FEVER

HENRY PINKERTON

THE PROTOTYPE OF THE DISEASES OF THE SPOTTED FEVER group (*Rocky Mountain spotted fever Eastern spotted fever fievre* boutonneuse tick bite fever São Paulo typhus) is Rocky Mountain spotted fever In recent years essentially similar diseases have been found to occur in many parts of the world All these diseases are tick borne but there are variations in the species of the tick vector and in the intermediate mammalian host Associated with these variations there are minor clinical and immunologic differences which have not been fully investigated Fievre boutonneuse which occurs chiefly in the countries along the Mediterranean shore differs immunologically from Rocky Mountain spotted fever sufficiently to justify regarding it as a true strain modification Brazilian spotted fever is described in the literature under the heading of São Paulo typhus It has not been demonstrated *that this disease differs in any significant way from Rocky Mountain* spotted fever and present evidence indicates that it is essentially identical with the latter disease Eastern spotted fever of the United States is likewise identical as far as our knowledge goes with Rocky Mountain spotted fever Tick bite fever of South Africa probably also belongs to the spotted fever group although Pijper and Crocker believe that it is a distinct entity

A description of Rocky Mountain spotted fever will be given and the few important individual features of the other strains and varieties will be pointed out under appropriate headings

Rocky Mountain spotted fever is an acute infectious febrile disease transmitted by ticks and caused by a *Rickettsia (Dermacentroxenus rickettsi family* RICKETTSIACEAE) *It is characterized clinically by an* incubation period of from four to eight days (extreme limits two to twelve days) onset with chills a continuous fever lasting from two to three weeks and terminating by lysis severe pain in muscles and bones headache and a characteristic macular eruption becoming petechial and involving the entire surface of the body including the palms and soles

HISTORICAL NOTE

The disease as well as its variant strains has probably existed since prehistoric times but was first described by Wood in 1896 and by Maxcy in 1899

Wilson and Chowning in 190 furnished evidence that the disease was trans mitted by the tick Ricketts in 1911 probably saw the etiologic agent in ticks and proved that the infection could pass from one generation of ticks to an other by actual infection of ova Wolbach in 1919 published his very complete and careful studies demonstrating the constant occurrence of intracellular *Rickettsiae* in the lesions of man monkey rabbit and guinea pig Wolbach also established the intracellular localization of the organism and in ticks the in tranuclear multiplication which is a unique feature of the spotted fever organism The constant presence of the organism in infective ticks and its absence from noninfective ticks were also established Wolbach named the organism *Dermacentroxenus rickettsi* believing that it differed sufficiently from *Rickettsia prowazeki* to warrant the use of a different generic name In 1930 the geographical range of the disease was extended by the discovery of spotted fever in the southeastern United States In 1931 spotted fever in Brazil was first described under the name of Sao Paulo typhus Monteiro Piza Meyer and Gomez carefully studied the disease from the clinical and experimental points of view and obtained clear cut evidence of its close re lationship to spotted fever It is probable that cases of the disease before the work of these investigators had been regarded as typhus Fièvre boutonneuse recognized since 1910 as somewhat different from typhus was not proved to belong to the spotted fever group until 1933

ETIOLOGY

D rickettsi is morphologically similar to *R prowazeki* but under some conditions the minute diploid forms are seen to be composed of more coccoid elements somewhat resembling minute pneumococci The staining reactions are identical with those of typhus *Rickettsiae* The tendency of *D rickettsi* to invade nuclei (Figs 49 and 50) in ticks and in mammalian tissue cultures is a unique cytologic phenomenon that is never seen in typhus The evidence for the etiologic relationship of the organism to spotted fever has been built up by methods almost identical with those described in detail in the case of typhus fever The biologic properties growth requirements and so forth also resemble those of *R prowazeki*

No morphologic cytologic or pathologic differences of importance have been demonstrated between the etiologic agents of the five diseases included in the spotted fever group Evidence that permanent variety changes may exist is based on certain rather definite clinical and immunologic differences Parker for example showed that although there was complete cross immunity in guinea pigs between fièvre boutonneuse and Rocky Mountain spotted fever a vaccine made from ticks infected with Rocky Mountain spotted fever which conferred complete protection on guinea pigs against the latter disease was in effective against fievre boutonneuse

EPIDEMIOLOGY AND GEOGRAPHICAL DISTRIBUTION

Spotted fever is almost invariably acquired from ticks either from the at tachment and engorgement of the tick or more rarely from contamination

of the fingers with infected viscera as a result of crushing engorged ticks There is some evidence that infection from tick viscera may penetrate the unbroken skin Infection by the conjunctival route is a possibility *Rickettsiae* are present

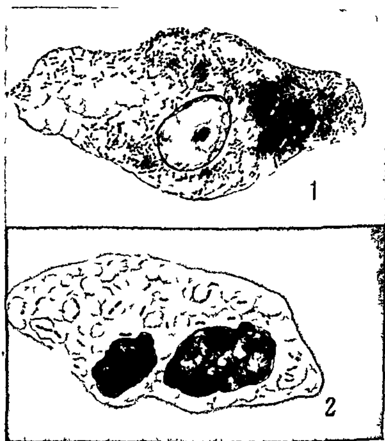
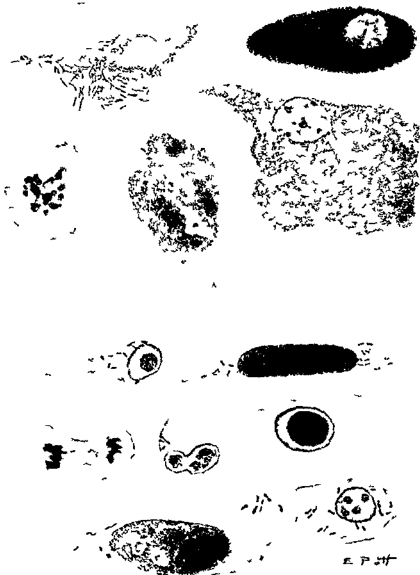


Fig 49 The differential diagnosis of typhus and spotted fever (1) Typhus rickettsiae and (2) spotted fever rickettsiae in smears from the scrotal sacs of infected guinea pigs The spotted fever rickettsiae are characteristically fewer larger and more diffusely distributed

in the salivary glands of the tick and are actually injected in the course of feeding Infection rarely results unless the tick remains attached long enough to become at least partially engorged This engorgement is believed by Parker to activate the virus

Since spotted fever infection is truly hereditary by way of infected ova and spermatozoa in ticks and since it does not harm the tick the virus can be perpetuated in nature without the intervention of the intermediate mammalian hosts although in Rocky Mountain spotted fever rabbits ground squirrels and other rodents undoubtedly act as a reservoir In fievre boutonneuse an important intermediate mammalian host is the dog It is probable that we have still much to learn regarding the possibilities of reservoirs of



Fi 50 Co ipa son of typl us nd sp tted f r k ttsi e in ti si e ultu e
A The typhu t ketts ae gr m s ly i the cytopla m but ever invade the nuclei
B Spotted feve icketts a grow most f eely i the cell nu le These patterns of cell in fection correspond to tho e see n the arth opod ctors namely the typhu lou e and the spotted f er t ck

diseases of this group The principal vectors of infection to man are as follows *Dermacentor andersoni* (wood tick) in western Rocky Mountain spotted fever *Dermacentor variabilis* (dog tick) in Rocky Mountain spotted fever in the eastern states *Rhipicephalus sanguineous* in fièvre boutonneuse and *Amblyomma cajennense* in São Paulo typhus Several other ticks are involved in transmission among lower animals and occasionally to man The rabbit tick *Dermacentor parumapestus* has been found to contain spotted fever virus of low virulence and since this tick occurs in a very wide geographical area it is probably an important factor in maintaining the virus in nature Random sampling of the tick population in various parts of the world has shown that as high as 11 per cent of the ticks are infected but in most areas only a small fraction of 1 per cent are found to contain the virus

Geographically the diseases of this group probably occur in all parts of the world where ticks engorge on human beings Unlike typhus spotted fever is primarily a rural disease its incidence coinciding with the warm weather tick season and never assuming epidemic proportions The highest incidence is in the spring and early summer and among individuals who spend much time out of doors

In the United States the greatest prevalence of the disease is in the Rocky Mountain area and in the southeastern states but cases have been reported from nearly all states The number of cases in the United States has not in recent years exceeded 500 annually In many areas heavily infested with ticks as on Cape Cod in Massachusetts very few cases of human infection occur because only a small percentage of ticks are infected The factors which determine the percentage of infected ticks in any one region and the variations in this percentage from year to year are not fully understood

Fievre boutonneuse differs somewhat epidemiologically from the other members of the group in that the dog is the intermediate mammalian host For this reason there is a greater tendency for the disease to occur in urban areas and even in individuals living in doors The total number of reported cases of fièvre boutonneuse is small but since the disease tends to be mild many cases are probably not recognized

In Sao Paulo typhus Diaz states that the dog is a probable reservoir while de Magalhaes has found the virus in nature in rabbits and opossums

PATHOLOGY AND PATHOGENICITY FOR ANIMALS

The pathologic picture of the disease in man is accurately reproduced by the experimental disease in guinea pigs rabbits and monkeys Rats and mice are practically insusceptible A scrotal reaction occurs with most strains in guinea pigs and in male human beings hemorrhage and necrosis of the scrotum are not infrequently seen The scrotal reaction in guinea pigs reacting to typical western Rocky Mountain spotted fever differs in type from that seen in murine typhus It is chiefly a hemorrhagic gangrenous lesion of the scrotum itself and is not usually associated with exudation in the scrotal sac Moreover its occurrence is independent of the route of inoculation whereas

the reaction in typhus occurs only after intraperitoneal inoculation In typhus actual gangrene of the scrotum is not seen Fièvre boutonneuse however and certain strains of eastern spotted fever show exudation in the scrotal sac similar in all respects to that of typhus

The gross and microscopic lesions in both man and experimental animals are remarkably similar to those seen in typhus The most constant gross differences are the much greater enlargement of the spleen in spotted fever and the occurrence of gangrene of the scrotum As in typhus the microscopic pathologic picture is primarily that of acute endangeitis involving the small blood vessels especially those of the skin and brain but thrombotic lesions are more numerous than those seen in typhus and necrosis of the fingers toes and ears is more frequently seen The endangeitis appears to be more severe and neutrophiles are more numerous than in typhus

The earlier studies of the disease both in man and in experimental animals failed to show focal brain lesions of the type seen in typhus and this was believed to be a distinguishing feature between the two diseases Lillie has recently shown however that focal brain lesions are commonly found in both man and guinea pig in reaction to eastern spotted fever and it seems probable that these lesions are about as constant in spotted fever as in typhus Lillie explains the previous failure to find them on the basis of the fact that the patients studied died before the lesions had time to develop There are minor but fairly definite differences between the brain lesions of spotted fever and those of typhus In the former small areas of focal demyelinization probably resulting from complete thrombotic occlusion of small arterioles are the most characteristic feature

Terminal bronchopneumonia is occasionally seen but in fulminating cases the chief cause of death is probably overwhelming toxemia

SYMPTOMATOLOGY

The clinical picture of spotted fever shows considerable variation depending largely on the severity of the disease but also to some extent on the strain involved As in typhus the disease tends to be milder in children than in adults but many severe and fatal cases occur in children Ambulatory patients with scanty atypical or even completely absent cutaneous lesions are occasionally seen It is particularly in the Rocky Mountain region that the acute fulminating type of the disease may be encountered The mild cases may have a duration of only a few days and in the absence of rash diagnosis can be only presumptive unless the disease is transmitted to experimental animals In most cases however the disease is sufficiently severe to be considered a serious illness the clinical features of which are well marked

The onset is sudden but there may be *prodromal symptoms* for from one to three days or longer The prodromal symptoms most often described are loss of appetite malaise irritability and chilly sensations Prodromal symptoms are probably more frequent than in typhus

The actual *onset* which is sudden is characterized by true chills sweating



A



B

Fig 51 Spotted fever showing the typical eruption with edema on the face hands and arms (Reproduced by permission of Drs José de Toledo Piza J R Meyer and Luis Salles Gomes Typho Exanthematico de São Paulo Sociedade Impressora Paulista São Paulo 1932)

backache pains in bones joints and muscles frontal or occipital headache conjunctival injection photophobia sensitivity of the eyeballs to pressure upper abdominal pain nosebleed nausea vomiting marked malaise and a



Fig 52 Spotted fever showing the typical eruption on the back and extending over the buttocks (Reproduced by permission of Drs José de Toledo Piza J R Meyer and Luis Salles Gomes Typho Exanthematico de São Paulo Sociedade Impressora Paulista São Paulo 1932)

dry non productive cough These symptoms are present in the early stages in various combinations of which headache muscle and bone pain and malaise are the most constant

The *rash* (Figs 51 and 52) appears between the second and sixth days after the onset of the disease It may be preceded by a mottled appearance of the skin In fulminating cases death may occur before the rash has time to develop The rash appears first on the wrists ankles or less frequently on the back or forehead and extends rapidly to involve the entire surface of the body including the palms and soles scalp and occasionally even the mucous membranes of the mouth and throat The early lesions are rose colored most often macular but occasionally papular disappearing on pressure in either case As the disease progresses the lesions become actual hemorrhages that no longer fade on pressure and the color changes from rose red to bluish or purple In mild and relatively favorable cases the lesions remain relatively large (3 to 6 mm in diameter) and considerable areas of intervening normal skin are seen Minute petechial at times almost coalescent lesions are characteristic of the more severe infections Successive crops of lesions a few days apart are occasionally seen especially in milder cases

In typical cases the *temperature* rises rapidly to 39.4° C (103° F) or higher and is maintained at a level between this and 40.5° C (105° F) for a period

of about two weeks falling gradually by lysis during the third week of illness. The height of fever is a better index of the severity of the illness than in typhus. In mild cases the maximum temperature may be 39.4 C (103 F) while in certain severe cases temperatures as high as 41.3 C (107 F) have been reported. Brief remissions especially in the morning are frequently seen but the temperature rarely becomes normal during these remissions.

In general the *pulse* rate follows the temperature but it may be disproportionately high. In severely toxic cases it shows a loss of strength and volume. *Respirations* usually range from 30 to 40 per minute but may be considerably higher in unfavorable cases whether or not bronchopneumonia develops.

Course of the Disease As the disease progresses restlessness and insomnia develop. The early pains in bones and muscles tend to disappear and evidences of toxemia develop but the extent of these depends on the severity of the illness. Stupor and delirium are common and in fatal cases coma usually but not invariably develops preceding death. Convulsions tremor opisthotonos ankle clonus and positive Babinski and Kernig signs are occasionally seen and are probably associated with the development of focal brain lesions. Slight albuminuria mild anemia and moderate leukocytosis with a count usually not exceeding 15 000 or 20 000 are the only *clinical laboratory data* which have been reported and these are of a non specific nature. The Weil Felix reaction is discussed on page 350. Abnormalities in the spinal fluid have not been reported.

COMPLICATIONS AND SEQUELAE

In the majority of cases convalescence is slow but uneventful. The most common complication is bronchopneumonia but occasionally lobar pneumonia may occur. Gangrene of extremities scrotum or buttocks is occasionally seen. Other less common complications are iritis acute nephritis hematuria and hemorrhage from the nose and intestinal tract.

Sequelae are not common although deafness impaired vision neurasthenia mental impairment and mental confusion have been reported. Although a strong and lasting immunity usually follows even a mild attack of the disease authentic second infections have been reported several years after recovery. There is no evidence for believing that the *Rickettsiae* persist in the body or that there are recrudescences such as have been believed to occur in typhus. In experimental animals infectivity of tissue disappears a few days after recovery.

CLINICALLY VARIANT STRAINS

In addition to the variant strains which have been given distinguishing names certain symptoms may be exaggerated or absent in outbreaks of spotted fever in different localities. The highly fatal strains are confined to the western states and often to small localized areas in these states. Parker states that the western strains are on the whole no more fatal than the eastern strains and the clinical picture shows no significant variation. Certain clinical differences in guinea pigs between the eastern and western strains have already been

described but the two appear immunologically identical even to the extent that vaccine prepared from western strains in *D andersoni* ticks give good protection against eastern strains in experimental animals

Sao Paulo typhus likewise duplicates clinically as far as can be determined the eastern and western strains of Rocky Mountain spotted fever

Fièvre boutonneuse is often characterized clinically by a primary lesion the tache noire at the site of the tick bite while in Rocky Mountain spotted fever and Sao Paulo typhus no local reaction occurs Usually also in fièvre boutonneuse there is an inflammatory reaction in the regional lymph nodes The local lesion is an indurated hyperemic painless and occasionally ulcerated button like lesion A similar local lesion is often present in South African tick bite fever Fièvre boutonneuse is clinically mild and the fatality rate is very low In guinea pigs also the disease is mild but careful morphologic studies have shown that it is otherwise identical with Rocky Mountain spotted fever Although there is complete cross immunity in guinea pigs between fièvre boutonneuse and Rocky Mountain spotted fever Parker has shown that vaccine produced from *D andersoni* ticks infected with the latter disease and giving complete protection in guinea pigs against Rocky Mountain spotted fever is ineffective against fièvre boutonneuse

DIFFERENTIAL AND LABORATORY DIAGNOSIS

Most of the conditions mentioned in the differential diagnosis of typhus may at times be confused with spotted fever but as the disease progresses the diagnosis except in atypical cases usually becomes clear A history of tick bite is of course an important diagnostic feature The early appearance of the rash its more hemorrhagic or purpuric nature and its tendency to appear first on the wrists and ankles and to involve the palms of the hands and soles of the feet (in contradistinction to the rash in typhus) are of greatest value Sulfanilamide dermatitis mentioned in connection with typhus (page 336) should be kept in mind Cases of streptococcus septicemia in which the organism gains entrance through the bite wound of a tick may raise a diagnostic problem which in the absence of a rash is solved by blood culture Cerebrospinal fever may need to be excluded by spinal puncture and measles the rash of which may simulate early spotted fever by the history the occurrence of coryza Koplik s spots and so forth

I have recently reported two cases closely simulating spotted fever both clinically and on microscopic examination of tissue post mortem but in which a proto oan parasite (toxoplasma) was established as the etiologic agent Such observations as this suggest that sporadic cases when sufficiently atypical to make a confident diagnosis on clinical grounds alone impossible should be studied by transmission to animals and other special laboratory methods Murine typhus and spotted fever frequently occur sporadically or endemically in the same geographical locations and it is often impossible to differentiate them without studies of the type already referred to particularly in cases in which the rash is poorly developed or even absent

Weil Felix Reaction The Weil Felix reaction is of great assistance not only in confirming clinical evidence but to a certain extent in distinguishing between typhus spotted fever and tsutsugamushi disease Agglutinations in spotted fever are characteristically in low titer with all three strains of *B proteus* while in typhus principal agglutinins are for OX19 and in tsutsugamushi for OXK as shown in the following table

	TYPHUS	TSUTSUGAMUSHI	SPOTTED FEVER
B proteus OX19	+++	−	+
B proteus OX2	+	−	+
B proteus OXK	−	+++	+

Agglutinins are usually present toward the end of the first week of fever and agglutination in a titer of 1 100 is probably significant especially if an earlier test has given negative results or agglutination in a lower titer

Skin Biopsy Skin biopsy is a valuable diagnostic procedure A well developed lesion preferably of the macular type should be excised with ample underlying tissue fixed in Regaud s fluid and stained by the Giemsa method The presence of *Rickettsiae* in the smooth muscle cells of arteriolar walls distinguishes spotted fever definitely from typhus in which *Rickettsiae* are present only in endothelial cells The recognition of *Rickettsiae* requires some experience

Transmission Test Transmission to guinea pigs is the most valuable single procedure in clinically doubtful cases Ten cubic centimeters of blood preferably during the first week of the disease should be withdrawn and 5 cc injected intraperitoneally into each of two large male guinea pigs Small guinea pigs should receive about 3 cc each The incubation period may be from four to twelve days or longer If scrotal swelling and redness take place the guinea pig should be killed transfers to other guinea pigs made and smears made from scrapings of the tunica vaginalis In typhus cells distended with *Rickettsiae* are seen in such smears whereas in spotted fever cells containing from one to twenty five or thirty scattered *Rickettsiae* are the rule If fever without scrotal reaction occurs transfers should be made There are a number of criteria which can be applied to the study of a rickettsial infection once it has been established in guinea pigs which enable an accurate diagnosis to be made Among these is cultivation of tissue culture which brings out the intranuclear clustering of the spotted fever *Rickettsiae* These tests are too technical for general use In atypical cases in which an accurate diagnosis is important the infection may be established in guinea pigs Infected guinea pigs should be sent to a laboratory equipped for further study Cross immunity tests with known strains of typhus and spotted fever are usually but not always sufficient to establish a definite diagnosis

Protection Test The protection test may be used to establish a diagnosis during convalescence or when the guinea pig infection tests fail because blood was taken too late in the course of the disease This test is carried out by mix

ing the patient s serum with infective doses of typhus and spotted fever material and injecting guinea pigs intraperitoneally together with suitable controls

PROGNOSIS

As we have already pointed out the prognosis depends on the type and severity of the infection The prognosis of fièvre boutonneuse is excellent but the mortality of Sao Paulo typhus approaches 80 per cent In certain regions in western United States the mortality may be 90 per cent or higher but from 15 to o per cent is usually given as an average figure The prognosis is considerably better in children than in adults and is generally poor in the aged Guides to prognosis during the course of the disease are the incubation period temperature pulse and respirations degree of toxicity and particularly the severity of the rash and the mental state (page 345) Previous vaccination especially if this has been carried out within twelve months of the onset of illness greatly improves the chances of recovery

TREATMENT

The treatment in general is that of any acute febrile illness Every effort should be made to conserve the strength and nutrition of the patient Avitaminosis should be guarded against and although the specific effect of riboflavin deficiency on experimental typhus has not been investigated in spotted fever vitamins of the B group should perhaps be given particular attention Careful nursing alcohol rubs tepid sponge baths frequent enemas forced fluid and an ice cap to the head are measures often recommended Digitalization if indicated and codeine for restlessness are probably important measures Differences of opinion exist regarding the advisability of morphine

Convalescent serum treatment has not been properly evaluated and the same may be said regarding the administration of the hyperimmune rabbit serum elaborated by Topping which is available in many localities

Sulfapyridine has been totally ineffective and possibly detrimental in laboratory animals infected with Rocky Mountain spotted fever by Topping Similar results (unpublished) but with even greater emphasis on detrimental effects have been obtained recently by Pinkerton and von Hofgaarden using sulfathiazole sulfadiazine neoprontosil fuadin and atabrine These drugs in the present state of our knowledge are definitely contraindicated except in the treatment of late bacterial complications such as pneumonia

PROPHYLAXIS

The avoidance of tick bites and care not to crush ticks in removing them from dogs sheep and other animals are obvious prophylactic measures Those who are compelled to work in tick infested territory should wear clothing designed for protection against ticks Tightly laced high boots and one piece costumes are of great help Since ticks are slow to attach themselves to human beings and do not begin to engorge for some time afterward considerable pro-

tection is attained by removing all clothing and searching the body thoroughly for ticks at frequent intervals If ticks are found attached they should be re moved carefully and the bite cauterized with crude carbolic acid introduced by means of a sharpened stick The chances of infection from an attached but unengorged tick are probably small

Extermination of mice is an important measure in reducing the tick popu lation of a given area since small rodents are necessary for the developmental stages of the tick (larvae and nymphs) Cleaning and cultivation of land are also of value

The vaccine of Spencer and Parker prepared from the tissues of ticks in fected with western strain of Rocky Mountain spotted fever is of recognized value and should be given about once a year to individuals working out of doors in tick infested regions where more than a rare single case has occurred Parker considers this vaccine to be equally effective against eastern and west ern spotted fever and in guinea pigs the vaccine is fully effective in protectin against São Paulo typhus (Brazilian spotted fever) Vaccination within twenty four hours of removal of an engorged tick is probably of some value particularly against the milder strains in which the incubation period is more often prolonged Infections occurring in properly vaccinated individuals have been significantly mild in type

Reasons for believing that the vaccine of Spencer and Parker would be in effective in man against fievre boutonneuse and quite possibly against other strains of spotted fever have already been brought out A more homologous vaccine however made from the strain involved could doubtless be used suc cessfully for any of the variant strains by the method of Spencer and Parker The egg yolk sac method of Cox apparently has many advantages for large scale production over the tick tissue method but it has not been actually ap plied on a large scale in practice

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CHAPTER XXVII

TSUTSUGAMUSHI DISEASE

HENRY PINKERTON

TSUTSUGAMUSHI DISEASE (RIVER FEVER, FLOOD FEVER, pseudotyphus, rural typhus, tropical typhus, type K) is an acute febrile rickettsial disease of variable severity transmitted by mites and characterized by an incubation period of from four to twelve days, a febrile course of from two to three weeks, a generalized papular or maculopapular rash, and often by an ulcerative and necrotic local lesion at the site of attachment of the vector, with swelling and tenderness of the regional lymph nodes.

HISTORICAL NOTE

The disease was first reported as a clinical entity in Japan in 1878 and was named flood fever or river fever because of its distribution along the course of large rivers in Japan. The recognition of the disease as a rickettsial disease was delayed until about 19 9, largely because of the difficulty of transmission to the usual laboratory animals by the ordinary routes of inoculation. Recognition of clinical variants of the disease in other countries is an even later achievement.

ETIOLOGY

The etiologic agent of tsutsugamushi appears from the published descriptions and illustrations to be morphologically very similar to *R. prowazeki* and to *D. rickettsi*, although possibly somewhat shorter and more diplococcoid than diplobacillary. It has been named *Rickettsia nipponica*, *R. orientalis* and *R. tsutsugamushi* by various investigators. The separation of this organism from *R. prowazeki* and *D. rickettsi* is based largely on the lack of evidence of cross immunity between these two organisms, although its low pathogenicity for experimental animals has made it difficult to carry out cross immunity tests in an entirely satisfactory way. The work of Lethwaite and Savoor on this problem seems, however, to indicate conclusively that tsutsugamushi disease is immunologically a distinct entity.

The methods available for isolating and studying the *Rickettsiae* of tsutsugamushi are (1) inoculation into the testis of the rabbit (Ogata and Unno)

and (2) inoculation into the anterior chamber of the eye of the rabbit (Nagayo) In the rabbit testis the organisms multiply in the cytoplasm of the interstitial cells where they can be clearly demonstrated in Giemsa stained smears and sections In the rabbit eye luxurious growth of *Rickettsiae* takes place in the corneal endothelial cells overlying Descemet s membrane Serial propagation of the infection is possible by either method Lethwaite and Savoor have recently been able to isolate and propagate a single strain of tsutsuga mushi (rural typhus) by intraperitoneal injection into guinea pigs in which resistance is lowered by vitamin deficiency They find however that this method is rarely successful with other strains An interesting feature of the infection produced in their deficient guinea pigs is the occurrence of peritonitis and ascites conditions not found in other rickettsial diseases

The occurrence of clinically variant forms of the disease in different locali ties has recently been recognized and the variations are of about the same type and magnitude as those seen among the members of the spotted fever group In so far as these various strains have been studied however no dis tinct immunologic differences have been brought to light It is of interest that in tsutsugamushi the strains associated with a severe local lesion at the site of the vector bite have the greatest severity and highest mortality while in the spotted fever group a local lesion is seen only in the milder strains (fievre boutonneuse and tick bite fever of South Africa)

EPIDEMIOLOGY AND GEOGRAPHICAL DISTRIBUTION

The disease is transmitted to man by the larval forms of the mites *Trombicula akamushi* and *T deliensis* and chiefly if not entirely by actual attach ment to the skin The adult and nymph forms of the mite are probably infective but do not feed on animals Cases of tsutsugamushi occur among individuals who spend their time out of doors in the country in contrast to typhus which is an urban disease In Japan infection takes place in dry regions where land is being cleared for cultivation The vole is held to be a mammalian reservoir for the virus in Japan while mice apparently harbor the virus in Sumatra Whether other mammals may harbor the infection or whether mites may maintain infection without an intermediate host has not been determined since no studies of the organism in the mite appear to have been made

The severe forms of the disease occur chiefly in Japan while the milder strains are more often encountered in Formosa Sumatra the Malay Peninsula the Bako Islands the East Indies and the Philippines It is probable that the geographical boundaries of the disease are incompletely determined since it may easily be confused with other rickettsial diseases unless careful laboratory studies are carried out

PATHOLOGY

There are no distinctive gross lesions The spleen is commonly enlarged and there is congestion of the viscera On the basis of the meager information

available the microscopic pathologic picture appears to be that of generalized endangeitis similar to the picture seen in spotted fever and typhus. The local lesion is an ulcer with coagulative necrosis healing by granulation tissue

SYMPTOMATOLOGY

As in spotted fever there may be mild *prodromal symptoms* consisting of headache dizziness malaise anorexia nausea and photopsia Since somewhat similar symptoms may apparently result in certain individuals from the bites of uninfected mite larvae (as a toxic manifestation) they are difficult to evaluate The typical true *onset* which is usually sudden and associated with a rise in temperature is characterized by various combinations of the following symptoms marked malaise headache conjunctival injection photopsia insomnia *a feeling of oppression pains in the joints dizziness hot flashes* and chills Constipation is the rule

A characteristic feature of the disease in Japan where the more severe cases occur is the *local lesion* at the site of attachment of the larval form of the mite The bite of this arthropod normally produces local swelling and redness, with some tenderness and pain on pressure but there is no necrosis The true local lesion of tsutsugamushi is a sharply defined pustule 2 or 3 mm in diameter which ruptures and leaves a rounded ulcer often attaining a diameter of from 6 to 8 mm with a black necrotic center and surrounding red areola This local lesion if it is to be present is usually seen at the onset of the disease and remains throughout the illness healing by granulation tissue and leaving a permanent scar

Associated with the local lesion which is most often seen in the genital and axillary regions but may be anywhere on the body there are marked swelling and tenderness of the regional lymph nodes During the course of the disease the lymphadenitis may become more generalized

The *rash* which appears between the fourth and seventh days of illness resembles that of the milder forms of spotted fever consisting at first of small papular or maculopapular lesions 1 to 2 mm in diameter appearing first on the trunk and then on the face These lesions remain discrete and enlarge to from 6 to 8 mm in diameter somewhat resembling those seen in *measles* As in spotted fever the cutaneous lesions in typical cases involve the entire surface of the body including the palms and soles and occasionally involving the mucosa of the mouth The cutaneous lesions do not itch and are not painful After from three to five days they gradually fade with slight desquamation

The temperature curve is characterized by a stage of invasion during which the fever rises higher each day for several successive days with morning remissions reaching 39 4 or 40 C (103 or 104 F) by about the third day Following this is a period of more sustained and higher temperature ranging up to 40 5 C (105 F) or higher in fatal cases and lasting from five to ten days The temperature falls by lysis during the last week of illness The pulse rate and respiratory rate are usually in proportion to the temperature but the

pulse may be relatively lower or relatively higher The respiratory rate is of course altered by secondary pulmonary infection which is not uncommon

During the course of the disease mental clouding or delirium may occur and coma may develop in fatal cases A dry hacking cough is usually present and the spleen may become palpable

In the *mild cases* and most of the cases occurring in countries other than Japan are of the milder type the clinical picture may depart widely from the typical one The local lesion is absent or inconspicuous lymphadenitis is ab sent and the systemic symptoms particularly the neurological symptoms are of a milder type In these cases it has been observed that the temperature rises more suddenly to its height but immunity appears to be established earlier and the temperature may fall rapidly after a few days Since the rash also may be absent in these cases the difficulty of making a diagnosis is obvious In these mild atypical cases transmission to rabbits by the intra-ocular or intratesticu lar route may be necessary in order to establish a diagnosis

Immunity in tsutsugamushi disease is apparently much less permanent than in typhus and spotted fever *Second attacks* may occur within a year of con valescence and although these are usually mild fatalities have been reported Mild second attacks of the disease in Japan may simulate the milder types which appear in other countries

COMPLICATIONS AND SEQUELAE

The most common complications are bronchopneumonia suppurative lymphadenitis gangrenous stomatitis and cystitis No true sequelae have been described and there is no evidence that recrudescences may occur

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis is made on the basis of the clinical picture with a history of exposure to mites and with the aid of the Weil Felix reaction (page 350) which usually shows agglutination with *B proteus* OXK Leukopenia is the only other feature of diagnostic importance The Weil Felix test unfortunately may be negative in mild atypical cases

The *differential diagnosis* includes spotted fever and typhus measles ty phoid and the various conditions discussed in the differential diagnosis of typhus and spotted fever In mild and atypical cases transmission to rabbits as already described may be necessary in order to establish a diagnosis

PROGNOSIS

In Japan the mortality rate varies from 30 to 60 per cent In many other regions such as the Malay Peninsula where the disease occurs without local ulceration or bubo the mortality is about 2 to 3 per cent As in other rickettsial diseases the prognosis is better in children and the mortality rate increases rapidly after the third decade The prognosis is better in the absence of a local lesion and of lymphadenitis and in the presence of high initial fever During the course of the illness the general condition of the patient particu larly with reference to nervous symptoms is the best guide to prognosis

TREATMENT

The principles of treatment do not differ from those detailed for use in spotted fever and typhus Immune serum therapy is in the experimental stages in all rickettsial diseases

PROPHYLAXIS

The most important general prophylactic measure is obviously the extermination of the mite Clearing and cultivation of land and destruction of voles mice and other possible mammalian hosts are also measures of importance Avoidance of mite bites by the use of chemical sprays and protective clothing are of value as personal prophylactic measures Spraying the ground with petroleum emulsion is said to be effective in killing the larval forms of the mite

The *Rickettsiae* of tsutsugamushi biologically resemble those of spotted fever and typhus and there is every reason to believe that vaccines could be prepared by the agar slant method and by the yolk sac method which have already been described Since the immunity is apparently rather transient however prophylactic vaccination would probably have to be repeated at *frequent intervals Cauterization of mite bites soon after detaching* the larvae might be effective but in the presence of numerous bites it would not be practical Excision of ulcers is of doubtful value

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CHAPTER XXVIII

TRENCH FEVER

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TRENCH FEVER (QUINTANA FEVER WOLHYNIA FEVER shin bone fever His Werner disease) is a non fatal but disabling specific louse borne febrile disease with an incubation period of from ten to twenty days (extreme limits of five to thirty eight days) It is characterized usually by sudden onset with fever headache and pain and soreness in the muscles bones and joints The duration is variable the initial attack which lasts from two to twenty five days is often followed by relapses over a period of several months The symptomatology is subject to marked variation

HISTORICAL NOTE

The disease was first recognized in 1915 when it appeared on both the eastern and the western fronts in Europe during the world war of that period Cases were extremely numerous and the total resulting disability assumed great importance Before the recognition of the disease as an entity it was customary to record cases as pyrexia of unknown origin There is some evidence that an endemic form of the disease had previously existed in Russia and it is probable that it has occurred in previous wars although no definite information on that point is available Our present knowledge of the disease is largely the result of investigations carried out by a British and an American commission during the war of 1914–1918 Following the war the disease apparently died out

The possibility of a recurrence of the disease during the present war is strongly suggested by recent reports of its occurrence in individuals on whom presumably normal lice were being fed in the process of manufacturing typhus vaccine by the Weigl method

ETIOLOGY

By feeding lice first on patients suffering from trench fever and then on human volunteers research workers were able to show that the disease could be transmitted from person to person by lice It was further shown that the dried feces of infected lice when rubbed into the scarified skin of volunteers pro-

duced typical trench fever with great regularity Louse feces remain virulent for several weeks or even months Lice became infected by feeding on febrile patients at any stage of the disease or in some instances even during convalescence as long as ten or twelve weeks after the termination of the febrile period Infection was also transferred from man to man by the intravenous injection of blood but not by rubbing blood into the scarified skin

Lice that were proved to be non infective and free from *Rickettsiae* commonly became infective about nine days after feeding on febrile patients and extracellular rickettsia like organisms regularly appeared in the intestinal tract and feces of such infective lice These organisms are similar to organisms occasionally seen in non infective lice but it seems probable that both virulent and non virulent forms of the extracellular organism seen in the intestines of lice may occur It is also possible that the similarity between the two forms the pathogenic and the non pathogenic is purely morphologic like that which obtains between the colon bacillus and the typhoid bacillus

Evidence for the etiologic relationship between an extracellular rickettsia like organism in the intestine of the louse and trench fever is strong but absolute proof of this relationship has not been furnished The organism appearing in lice fed on patients with trench fever has been named *Rickettsia wolhynica* and *R quintana* while the organism seen at times in apparently normal lice was called *R pediculi* by Munk and da Rocha Lima It is possible that these two organisms are identical

Further study of the etiology of trench fever is much to be desired Unfortunately transmission to experimental animals was not accomplished during the war of 1914–1918 and since the disease disappeared shortly after the war practically no progress has been made in the study of trench fever since that time

EPIDEMIOLOGY AND GEOGRAPHICAL DISTRIBUTION

The disease as far as our knowledge goes is confined to Europe but it is not unlikely that it might appear anywhere in the world if extensive louse infestation were allowed to occur There is no evidence of the existence of any intermediate mammalian host but appropriate studies for discovering such a host have not been carried out and it will be remembered that the discovery of an intermediate host for typhus was not made until 1930 The long persistence of the infective agent in the blood of clinically recovered patients makes the assumption of an intermediate host unnecessary *R pediculi* has been shown to be transmitted in lice from one generation to another by infection of the ova and although similar observations were not made for *R wolhynica (quintana)* it is possible that infection may persist in lice for long periods of time

PATHOLOGY

Since the disease is not fatal and has not been transmitted to animals nothing is known concerning the systemic pathologic changes Skin biopsy has

shown no specific changes and *Rickettsiae* have not been demonstrated in human skin

SYMPTOMATOLOGY

Prodromal symptoms consisting chiefly of headache and malaise may occur at any time during the incubation period The *onset* is usually sudden with severe headache chills and fever and marked anorexia The headache is usually localized behind the eyeballs Severe pain and tenderness in muscles and bones particularly in the lumbar region and legs is a characteristic feature of the disease and is probably responsible for the name shin bone fever Abdominal pain and tenderness may occur but are usually bilateral and are more marked on gentle than on firm pressure Pain on rotating the eyeballs together with conjunctivitis and photophobia is usually noted in typical cases Mild laryngitis and bronchitis are not uncommon and nausea and vomiting may occur

In a few cases the onset is insidious and the course prolonged and mild the symptoms consisting chiefly of neurasthenia and tachycardia

The *rash* consisting of red macules 2 to 10 mm in diameter is nearly always present in typical cases and appears within a few hours after the onset of the fever In abortive cases however it is believed that the rash may be absent It lasts as long as the fever persists and recurs with recurrent attacks of fever The lesions appear first on the chest and abdomen and are usually confined to those regions but may involve the entire trunk and occasionally the extremities The face is not involved

The *temperature* is irregular and variable and may take a number of different forms Abortive attacks lasting only or 3 days are not uncommon There may be prolonged continuous fever of 2 or 3 weeks duration The fever is rarely of high grade usually not exceeding 39 6 C (103 3 F) Often the temperature drops to normal on the third fourth or fifth day but rises again within twenty four hours and remains elevated for several more days With late relapses the temperature usually rises again

The *pulse* rate usually follows the temperature during the initial acute attack but marked tachycardia may develop with relapses

The *course of the disease* is remarkably variable as suggested by the feature of irregular recurrent temperature The spleen usually becomes palpable Regardless of the severity of the original attack *relapses* often occur weeks or months later and in rare instances even several years later These relapses are usually associated with the recurrence of all the original symptoms and of the characteristic rash

COMPLICATIONS AND SEQUELAE

Complications of importance have not been described The most important sequela is a neurasthenic state with tachycardia and dyspnea on slight exertion In certain cases this picture may develop without an antecedent acute attack More or less permanent lumbar pain is a common complaint in the more chronic form of the disease

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

In the early stages and particularly in the atypical abortive cases the disease may be confused with influenza or other acute infections In typical cases *the diagnosis is usually clear from the clinical picture particularly* the early appearance of the rash and its tendency to come and go with fever and subjective symptoms The lack of mental symptoms or other evidence of severe toxicity is also important in excluding typhus typhoid and spotted fever together with the results of agglutination tests blood culture and so forth Relapsing fever and malaria may be ruled out by examination of suitably stained blood films In chronic cases with tachycardia fatigue and evidence of neurasthenia accurate diagnosis may be impossible and during the war of 1914–1918 there was perhaps too great a tendency to diagnose such cases as trench fever without adequate evidence The similarity of these cases however to those in which a preceding attack of typical trench fever was observed made the diagnosis of trench fever appear highly probable

PROGNOSIS

The disease is never fatal but causes marked and relatively prolonged disability About 85 per cent of all patients are able to return to work within two months of the onset of the disease In about 5 per cent of all cases the chronic form of the disease develops and recovery may not be complete for many months In spite of this fact it has not been demonstrated that resistance to other infections such as tuberculosis is lowered

TREATMENT

The patient should remain in bed should be given careful nursing and attention should be paid to his diet The pain and discomfort usually respond to acetylsalicylic acid phenacetin and similar drugs but codeine may be required Morphine is rarely if ever indicated but hypnotics may be safely used to control insomnia Care is of particular importance during convalescence and a period of from seven to ten days following the disappearance of symptoms and fever should elapse before the patient returns to work Relapses should be watched for and treated early with further hospitalization

PROPHYLAXIS

The prophylaxis of trench fever is obviously the avoidance of louse infestation and the avoidance of contact with louse feces In hospitals the same measures for delousing patients and for avoiding contact with lice which have been described in the prophylaxis of typhus fever should be carried out Autoclaving of clothing and blankets which may be contaminated with louse excreta is of particular importance because of the prolonged viability of the infective agent in the dried state Rubber gloves should be worn when handling clothing and blankets which may be soiled with louse feces Since the urine and sputum are believed to be infective these should be disinfected chemically or by heat

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CHAPTER XXIX

Q-FEVER

HENRY PINKERTON

Q-FEVER (AUSTRALIAN Q-FEVER AMERICAN Q-FEVER nine mile fever) is an acute febrile disease with a duration of from six to twenty four days characterized by headache malaise anorexia pain in the back and extremities and evidence of atypical pneumonia The incubation period has not been accurately determined but is believed to be about one or two weeks in most cases Since the disease is a recently recognized one the clinical picture may be regarded as still in the process of formation The possible identity of the disease with a type of atypical pneumonia which has been reported in various localities in recent years should be kept in mind

HISTORICAL NOTE

Q fever in Australia was first described by Derrick in 1937 chiefly among individuals working in slaughterhouses or as dairy farmers Burnet and Freeman described a rickettsia like organism in smears of the spleens of infected mice This organism was named *Rickettsia burneti* by Derrick A similar organism was recovered by Davis and Cox from ticks (*Dermacentor andersoni*) collected in Montana This organism was found to be pathogenic for guinea pigs and its properties were carefully studied before there was any indication that it might be related to human illness This organism was called *Rickettsia diaporica* Dyer in 1938 reported a case of accidental laboratory infection with *R diaporica* and showed that there was cross immunity between Australian Q fever and the Montana infection in guinea pigs This observation has been confirmed and careful comparison of the two organisms *R burneti* and *R diaporica* has shown that they are closely related if not identical Minor differences in behavior in guinea pigs not unlike the differences described in various strains of spotted fever have been observed but no differences which are inconsistent with the fundamental similarity of the two organisms The Montana infection was called nine mile fever before its similarity to Q fever of Australia was recognized

There have been several cases of laboratory infection both in Australia and in the United States and recently an institutional outbreak occurred in Washington D C

ETIOLOGY

The etiologic relationship of *R burneti* and *R diaporica* to Q fever in Australia and in the United States respectively has been established by guinea pig inoculation and serologic tests Workers in both countries have studied the biologic properties of the organisms and have found that they are filterable through Berkefeld filters which apparently do not allow typhus and spotted fever *Rickettsiae* to pass

Morphologically the *Rickettsiae* of Q fever are similar to those of spotted fever and typhus but they appear to be somewhat larger (perhaps because they stain more deeply) The organisms in infected animal tissues apparently grow both intracellularly and extracellularly Within infected cells which are chiefly mesothelial and reticulo endothelial cells the organisms tend to form compact spherical clusters the pattern of infection being quite similar to that of *Bartonella bacilliformis* Growth occurs both intracellularly and extracellularly in the various media containing living cells that are commonly used for the growth of *Rickettsiae* and filterable viruses Growth has not taken place in any cell free medium

Although they differ from more typical *Rickettsiae* in not being obligate intracellular parasites the tentative classification of the organisms of American and Australian Q fever with the *Rickettsiae* seems most useful and logical on the basis of our present information particularly in view of their permanent residence and transmission from generation to generation in ticks

EPIDEMIOLOGY AND GEOGRAPHICAL DISTRIBUTION

One definite reservoir of infection is known to be the tick *D andersoni* The existence of intermediate mammalian hosts is probable but this question requires further work There is evidence that the bandicoot (a marsupial) may harbor the infection in Australia

The mode of transmission to man is still obscure Because most of the cases in Australia occur among workers in slaughterhouses Derrick made an attempt to recover the infection from the meat of cattle and sheep These experiments gave negative results but were perhaps not entirely conclusive Transmission to man by tick bite is a strong probability While investigations were being conducted on a number of laboratory infections in Australia evidence was obtained that infection might possibly be carried from man to man by the mites *Lyponissus bacoti* (Hirst) and *L bursa* (Berlese)

From a survey of the circumstances attending the outbreak in the National Institute of Health at Washington D C it seems not unlikely that direct droplet infection from person to person may occur although there is no definite proof of this If infection by the respiratory route can occur the possibility of serious epidemics must be considered

The geographical distribution of cases thus far reported—Queensland (Australia) Montana and Washington D C—probably gives no indication of the true situation

PATHOLOGY AND PATHOGENICITY FOR ANIMALS

In one human case reported by Lillie Perrin and Armstrong the gross pathologic findings showed pulmonary edema and congestion firm granular consolidation of the upper lobe of the right lung posteriorly and a large soft spleen The other organs showed no important changes Microscopically the picture in the lung was that of an atypical pneumonia with much fibrin in the alveoli and bronchioles and in general a scanty mononuclear cell reaction instead of the purulent reaction seen in typical bacterial pneumonia Similar *pathologic changes were seen in the lungs of experimentally infected* monkeys In neither the human nor the monkey lungs were *Rickettsiae* demonstrated histologically The similarity of the pathologic picture to that described in fatal cases of atypical pneumonia of unknown origin by Longcope and by Kneeland and Smetana was striking The picture is also rather similar to that of certain cases of psittacosis pneumonia

In guinea pigs no pathognomonic histologic findings have been described. After an incubation period of from two to eighteen days depending on the amount of infective material injected guinea pigs react with fever for from four to six days and with loss of weight and appetite Guinea pigs have been successfully infected by the inoculation of human blood or urine There is practically no mortality in guinea pigs but when the animals are killed and smears of the spleen are made a large soft spleen is found and *Rickettsiae* may be seen both free and in mononuclear cells The smears should be stained by either the Giemsa or the Machiavello method

In mice Burnet and Freeman describe small necrotic foci in the liver and the presence of *Rickettsiae* in the Kupffer cells

SYMPTOMATOLOGY

On comparing the clinical picture of the nine cases reported by Derrick in Australia with that of the fifteen cases reported in Washington D C by Hornibrook and Nelson we are struck by the essential similarity between the Australian and the American cases The American cases however were reported as cases of pneumonitis while the pulmonary involvement was not stressed in the Australian cases only two of which had cough and only one of which had clinical evidence of pulmonary consolidation while rales were heard in only two Eight of the fifteen American cases had cough but expectoration was present in only three and respirations were not markedly increased in any The existence of pulmonary consolidation would probably have been overlooked in the American cases if x ray examination (Fig 53) had not been made Roentgenological evidence of pneumonitis was present in all but one of the American cases Since there is no report of x ray examination in the Australian cases it seems probable that pneumonitis may have been overlooked

The clinical description to follow will be based on both groups of cases with the assumption that they are the same disease

Prodromal symptoms of a vague nature are described but the actual *onset* is fairly sudden although not associated with severe symptoms so that the patient may continue work for several days Two types of onset are described



Fig 3 Q fe er Roentgenogram of the lun s (Publ c H lth R po ts Vol October 2 1940)

in the American cases one coryza-like and the other with headache chilly sensations and general malaise Only the latter type of onset was described in the Australian cases and the onset with coryza was seen in only four of the American cases The onset was associated with chills in four cases in each series

Temperature ranging from 38 3 to 40 , C (100 9 to 105 4 F) is usually present throughout the illness daily remissions of any considerable degree

being unusual In several cases the temperature has fallen after about two weeks only to rise again three days later remaining elevated for another week In the milder cases the temperature falls rapidly by crisis between the sixth and tenth days but in more severe cases the fever is prolonged (up to twenty five days) and falls by lysis over a period of several days

The *pulse* is relatively slow in proportion to the temperature rarely going above 110 and usually not exceeding 100 *Respirations* in spite of the pul monary involvement have not exceeded 28 Mild cyanosis was present in one case

Rash does not appear to be a prominent feature Two of the Australian cases had a few red spots on the abdomen at the time of admission and one case developed a definite punctate red rash first on the back and later on the chest and abdomen This rash appeared on the fourteenth day of illness and lasted only about forty eight hours It is of interest that an occasional case of atypical pneumonia of unknown origin has developed a rather similar rash

Mental symptoms are not common but in several of the more severe cases drowsiness and even stupor were observed

Course of the disease As has already been mentioned most of the cases show a rather mild course but occasionally the illness is prolonged and severe Pneumococci which can be typed are not found in the sputum and all the usual agglutination tests including the Weil Felix reaction are negative In somnia flushed face and conjunctivitis are prominent symptoms Vomiting epistaxis and jaundice are irregularly observed The white blood cell count is rarely elevated and often low and a moderate relative or absolute lympho cytosis is occasionally seen

COMPLICATIONS AND SEQUELAE

Insomnia thinning of the hair general weakness and prolonged anemia are the only persistent sequelae which have been described and these are the ex ceptions rather than the rule

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis is to be suspected on the basis of the clinical picture The most important feature is probably the presence of roentgenographic evidence of pneumonitis (Fig 53) with absent or scanty physical signs

The *differential diagnosis* from influenza may be very difficult in cases which show coryza at onset and run a mild brief course Other conditions to be con sidered in the early states are typhoid typhus paratyphoid undulant fever and leptospirosis all of which are readily ruled out by agglutination tests and other well recognized procedures

As we have previously indicated the clinical picture in practically all de tails is strikingly similar to that of atypical pneumonias described by Long cope Kneeland and Smetana Reiman and a number of other observers There are also basic pathologic similarities between these atypical pneumonias and Q fever pneumonitis Curiously however three other etiologic agents have

recently been shown to produce similar clinical and pathologic pictures namely (1) a virus obtained by Weir and Horsfall by inoculating the mongoose with sputum from human cases of atypical pneumonia (2) an atypical strain of psittacosis virus (Eaton Beck and Pearson) and (3) a protozoan parasite *toxoplasma* (Pinkerton and Henderson)

For this reason it is of particular importance at present that a definite diagnosis be established in cases of illness presenting this picture Q fever can be definitely diagnosed by transmission to guinea pigs (inoculation of blood or urine intraperitoneally) and by agglutination tests psittacosis by the intracranial injection of filtered sputum in mice as well as by the complement fixation test and toxoplasmosis by injection of blood into guinea pigs and mice

Once established in guinea pigs Q fever *Rickettsiae* are recognized by their appearance in Giemsa stained films from the spleen

PROGNOSIS

The prognosis in the more common mild cases is excellent Death occurred in only one of the American cases Convalescence is rapid in the mild cases but may be prolonged over a period of several months in the severe cases

TREATMENT

In the present state of our knowledge treatment is supportive and symptomatic Sulfapyridine has been found apparently ineffective in the human cases and sulfarsphenamine had no effect on the course of the illness in guinea pigs

PROPHYLAXIS

Avoidance of tick bites and possibly mite bites is probably important in personal prophylaxis If as seems quite possible the disease is transmissible from person to person as an influenza like respiratory infection the same precautions as those taken against the spread of colds and influenza should be employed Experimental evidence that vaccination with killed *Rickettsiae* may be effective and practical has been furnished by Cox

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CHAPTER XXX

VERRUCA PERUANA

HOWARD FOX

VERRUGA PERUANA (OROYA FEVER, CARRION'S DISEASE, bartonellosis) is an infectious disease caused by *Bartonella bacilliformis*. This organism has been cultivated and inoculated successfully in certain animals and is transmitted by several night flying species of *Phlebotomus*. There are two strikingly different types or phases of the disease: (1) verruga, which presents a characteristic eruption followed nearly always by complete recovery, and (2) Oroya fever, which is characterized by severe constitutional disturbances including anemia of the pernicious type and which in adults frequently causes death. Recovery from either form of the disease is probably followed by permanent immunity. For many years the disease was thought to be confined to some areas of Peru, but recently it has been observed in Colombia and Ecuador. Treatment is symptomatic, as no specific remedy is known. Prophylaxis is all important.

HISTORICAL NOTE

Verruga peruana has probably existed in Peru for centuries. It is said to have been the cause of the death of one fourth of the army of Pizarro, the Spanish conqueror. Little was known about verruga peruana before 1870, when a railroad was built over the Andes from Lima to Oroya. This was the cause of a terrifying epidemic during which it is said that 7,000 workmen died. It might be added that they were largely Chileans who, though physically stronger than the Peruvians, were not immune to the disease. Of the one hundred British and American engineers who constructed the railroad, all contracted the disease and half of them died of it. Even as late as 1935, when the method of prevention was well known, there was a mild epidemic among the laborers who built an automobile highway paralleling the railroad.

The disease which appeared in 1870 was called Oroya fever because the town of Oroya was the eastern terminus of the railroad where many of the victims were taken. The name was not especially appropriate, as the disease had never been contracted in Oroya. Opinions differed regarding the nature of this disorder. Some authorities thought that it was a modified form of malaria, others thought it an entirely new disease, while still others considered it to be

a severe type of verruga peruana an opinion which was later substantiated

The opinion that Oroya fever and verruga were different types of the same disease gained ground and was finally settled in the minds of the Peruvian physicians by the experiment of a brilliant medical student Daniel A Carrion Against the advice of his friends this young enthusiast in 1885 allowed himself to be inoculated on the arms from a patient suffering from verruga. Unfortunately he contracted the severe Oroya fever type and died at the end of thirty nine days The experiment of Carrion at least proved that the disease was inoculable in man and that verruga and Oroya fever were probably different phases of the same disease Absolute proof of this was possible in later years after artificial cultivation of the organism had been attained

In 1913 the Harvard commission under the leadership of Strong studied the disease in Peru and came to the conclusion that verruga and Oroya fever were separate diseases (This opinion carried great weight in the scientific world because of the high reputation of the five members of the commission *In the course of their studies they successfully inoculated a volunteer with* verruga who contracted the same mild type of the disease) In arriving at their conclusions the commission stated that no accurate record of Carrion's case was available and that no necropsy had been performed Unfortunately they did not see the detailed account of Carrion s illness and autopsy which was published by Alcedon in 1905 as otherwise their conclusions might have been different

ETIOLOGY

The causative organism was discovered in 1905 by Alberto Barton He observed these organisms in the erythrocytes of two patients suffering from the Oroya fever type of the disease In 1909 after further experience he stated that the organisms were probably protozoa and were the causative agents of the disease Strong later named the organism *Bartonella bacilliformis* in honor of Dr Barton

B bacilliformis is found in the red blood cells appearing as rod shaped or round bodies in preparations stained by Giemsa s method The rod shaped bodies vary from 1 to 2 microns in length and from 0 2 to 0 5 micron in width They occur singly in pairs or in end to-end chains often assuming a V or a Y form Dumbbell forms predominate and the two poles often show a more intense stain than the intervening parts The round forms vary in diameter from 0 3 to 1 micron and occur singly in pairs or in groups With darkfield illumination *Bartonellae* show motility as first demonstrated by Strong and his co-workers

The number of organisms in the erythrocytes varies from one to ten or more They are found not only in the peripheral blood but also in many of the tissues including the lymphatic glands liver spleen intestines and cutaneous lesions They are seen at times in nucleated red blood cells and on rare occasions have been observed in the leukocytes of the blood

Opinions differ as to the proper classification of *Bartonella* Some have

thought that the organisms were protozoa while Noguchi considered them to be bacteria The present tendency is to classify *Bartonella* with the *Rickettsiae* They are both minute pleomorphic gram negative organisms which in the human body are intracellular Both of them are usually transmitted by arthropods

It might be mentioned that in recent years other species of *Bartonella* have been discovered in certain animals some as pathogens and others as harmless parasites These include *B muris* first observed by Mayer in 1921 and other species which affect rats dogs monkeys and other mammals

Cultures It has been stated that *B bacilliformis* was first cultivated by Battistini and independently by Hercelles in Peru in 1925 It is generally thought however that pure cultures on a semisolid nutrient medium were probably first obtained in 1926 by Noguchi and Battistini working at the Rockefeller Institute The successful cultivation of the organism made it possible through animal inoculations to prove beyond all doubt that verruga peruana and Oroya fever were merely different phases of the same disease A specimen of citrated blood from a case of Oroya fever was sent from Peru to New York from which Noguchi eventually secured a pure culture on his *Leptospira* medium By inoculating rhesus monkeys on the eyebrows he produced verruga lesions and obtained pure cultures from the blood of these animals In the following year Mayer and Kikuth inoculated rhesus monkeys with material from a human case of verruga They not only produced verruga lesions in monkeys but demonstrated *Bartonellae* in the blood of some of them and reproduced the picture of Oroya fever which resulted in death in two of these animals Thus Noguchi reproduced verruga from the blood of an Oroya fever patient while Mayer and Kikuth reproduced Oroya fever from human verruga lesions

B bacilliformis is a gram negative motile obligatory aerobe It was grown by Noguchi on his *Leptospira* medium and on blood agar even in a dilution of 1 10 000 Pinkerton and Weinman (1937) grew the organism in tissue cultures and Jiminez and Buddingh obtained good results with the use of the developing chick embryo

The first successful transference of the disease to animals was made in 1910 by Jadassohn and Seiffert who inoculated monkeys and carried the infection through three passages Experimental infection of animals has usually been made by inoculation of material from verrugous lesions less often by culture and almost never by blood even when it contained great numbers of *Bartonellae*

Human inoculations Mention has been made of the fatal experiment of Carrion and of the volunteer who was inoculated by Strong and his co-workers Carrion was inoculated with material from the relatively harmless type of the disease (verruga) and died of the severe Oroya fever type Since then Peruvian physicians have been opposed to further human inoculations believing that the unity of the two types of the disease has been reasonably demonstrated

Unlike Carrion the volunteer inoculated by Strong with material from lesions of verruga developed only lesions of verruga with no appreciable anemia and absence of *Bartonellae* in the blood From this experience it was concluded that direct inoculation of the verruga virus from man to man does not produce Oroya fever It merely proved however that inoculation of verruga in man was capable of producing verruga

The reverse of Carrion s memorable experiment was shown by a physician of Peru who was accidentally inoculated with *Bartonella* from a patient with Oroya fever to whom he was giving a blood transfusion He subsequently developed typical verruga the eruption disappearing at the end of ten months

EPIDEMIOLOGY AND GEOGRAPHICAL DISTRIBUTION

Until recently it has been thought that verruga peruana was confined not only to Peru but certain areas in that country on the western slope of the Andes In Peru the disease occurs in narrow ravines or canyons (*quebradas*) at altitudes which are approximately between 2 500 and 9 000 feet It does not occur in the coastal or high mountainous regions In the affected areas the vegetation is fairly luxuriant and there is considerable heat during the day though the nights are rather cold

For some years there have been unverified reports of the presence of the disease in neighboring countries of Peru There was a possible epidemic of verruga in Colombia in 1936 where the mortality rate was 40 per cent with 1 800 deaths The first complete report from both clinical and bacteriologic standpoints of the presence of the disease outside of Peru (in Colombia) was published by Patino-Camargo in 1939 The disease has also been recently recognized in Eucador

Verruga peruana occurs in both sexes in all races and at all ages It may appear in the newborn when it is said to be severe A single case of intrauterine infection is quoted by Odriozola Most of the inhabitants of endemic areas have suffered from the disease in childhood According to Gomez in children up to ten years of age the infection is mild it becomes severe in adolescence or adult life Five infants from eight to nine months of age whom I saw in the Rimac valley (near Lima) presented typical but extremely sparse eruptions and appeared to be in good health In no instance was there a history of constitutional symptoms except for a day or two of malaise or fever All non immune visitors to endemic areas are subject to infection if they spend one or more nights in the ravines without taking proper precautions against the bites of sandflies The majority of infections occur between January and April when the streams are flooded the air is moist and still and insect life is abundant

Transmission Although Arce in 1889 first suggested that some blood sucking insect was the vector of the disease the first extensive investigations were made in 1912–1914 by Townsend who worked for two years in the Rimac valley He concluded from entomologic evidence that the disease was transmitted by a species of sandfly which he named *Phlebotomus verrucarum* He was ap-

parently able to exclude other common blood sucking arthropods as vectors

The work of Townsend was later confirmed by Shannon who discovered a second species of sandfly and named it *Phlebotomus noguchii* in recognition of Noguchi s able researches in this disease He said that *P verrucarum* appeared to be mainly a domestic species whereas *P noguchii* lived out of doors This explained why the disease was contracted either indoors or outdoors at times miles away from any habitation

There have apparently been no attempts to transmit the disease to man from a living insect However it has been transmitted to monkeys by allowing the animals to be bitten by sandflies or by inoculating them with the crushed insects

Human beings suffering from active manifestations probably constitute at least one source of infection It is also possible that persons showing no symptoms of the disease may also act as reservoirs of the parasites as *Bartonellae* have been demonstrated in the blood and positive cultures obtained from such persons It is also possible that certain animals may play the same role though this has not been proved

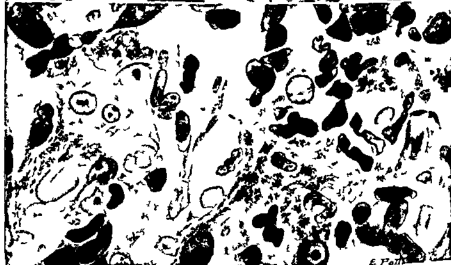
It has been suggested that certain plants may act as reservoirs In a botanical survey in 1930 of canyons where the disease was endemic Maldonado found that certain lactescent plants had the same habitat as that of the sandflies He failed to find these plants in non infected regions He thought that this fact suggested that these plants might serve as a reservoir of the organisms and also as food for the insect vectors In 1933 Mackehenie and Coronado obtained under aseptic precautions from the latex of these plants cultures of organisms apparently identical with *Bartonella* Agglutination was obtained in these cultures by serum from a convalescent case of verruga in a dilution of 1 1600

PATHOLOGY

According to Hercelles the principal changes which are constantly seen in the Oroya fever type of the disease are hemorrhage and thrombosis Such changes may be seen in most of the tissues and organs of the body *Bartonella* (Fig 51) has been obtained in cultures from most of them especially the spleen kidneys lymphatic glands and bone marrow The histologic structure of the cutaneous lesions according to Strong and his co workers may have either a sarcomatous a myxomatous or angiomatous (cavernous) appearance Da Rocha Lima states that the basic process in the formation of verruga tumors is a growth of vascular elements Cole who studied the comparative histology of verruga in man and apes considered the process to be a granuloma with special changes characterized by dilatation of lymph vessels filled with mononuclear and polymorphonuclear leukocytes He also found a perivascular infiltration composed mainly of plasma cells fibroblasts and mononuclear leukocytes with the formation of many new capillaries edema and extravasation of blood in the tissues

Weiss speaks of the two phases of the disease as hematic and histioid The former is characterized by the presence of *Bartonellae* in the blood In the

A



B

Fig. 51. A. Liver from a fatal case of Oroya fever (anemic form of Carrion's disease) showing *Bartonella bacilliformis* in the Kupffer cells and also in the red blood cells. Regaud fixation and Giemsa stain. × 1100.

B. Cutaneous nodule from a case of verruga peruana (cutaneous form of Carrion's disease) showing *Bartonella bacilliformis* in the proliferating endothelial cells. Regaud fixation and Giemsa stain. × 1100. Original drawing by Pinkerton.

histioid type the activity of the organism is limited to the reticulo-endothelial system He considers the appearance of the verrugous lesions to be an allergic reaction

SYMPTOMATOLOGY

There are two clinical forms of Carrion s disease which warrant separate descriptions namely (1) Oroya fever and (2) verruga peruana Between these two classical types however there are innumerable gradations

Oroya Fever or Malignant Type The period of incubation was estimated by Odriozola to be between fifteen to forty days In the case of Carrion s experimental inoculation it was twenty one days After a prodromal period of malaise and headache there is a sharp rise of temperature associated with chills The fever is of the remittent type and the temperature varies between 38 to 39 C (100 4 and 10 2 F) rarely going above 40 C (104 F)

The characteristic feature is rapid and severe anemia of the pernicious type The red blood cells may fall as low as 1 000 000 or even less within three or five days though this occurs more often at the end of one or two weeks There is probably no other condition except hemorrhage which can cause such a sudden and tremendous fall in the number of the erythrocytes The blood contains both normoblasts and megaloblasts and in some cases all the bizarre types of cells which are seen in pernicious anemia As a rule there are large numbers of *Bartonellae* in the blood According to Monge the anemia is due to a disturbance in the regenerative power of the blood and not to destruction of the red blood cells he thinks there is neither hemorrhage nor evidence of hemolysis in proportion to their diminution

There is also a disturbance of the white blood cells There is a leukocytosis at times with a count of 20 000 the eosinophiles disappear and myelocytes and myeloblasts may be present

The clinical picture is most distressing to witness The patient suffers from severe pain in the muscles and joints nausea and vomiting and unquenchable thirst and frequent attacks of syncope after merely sitting up in bed There may be bleeding from the nose and hemorrhage in the skin in the form of petechiae Delirium and coma follow and death may occur within a few weeks after the onset of fever Estimates of mortality vary from 30 to 90 per cent 40 per cent being probably a fair average

Verruga Peruana or Benign Type The period of incubation of the benign type is not definitely known but it appears to be similar to that of the Oroya fever type In experimental inoculations in animals it varies from eight to sixty days In the experiment of Kuczynski who inoculated himself with a culture of *Bartonella* the incubation period was seventeen days The course of this type of the disease may be divided into (*a*) the stage of invasion and (*b*) the eruptive stage

The invasive stage is ushered in with constitutional symptoms including a mild fever usually of intermittent or tertian type simple anemia gastro-intestinal disturbances and more or less severe pain in the muscles and joints

Bartonellae may or may not be present in the blood but when present they are always much fewer in number than in the Oroya fever type The invasive stage lasts from three to four months and when the eruption appears the con



FIG 55 Verruga peruana Profuse eruption of miliary type of three months duration in a white man 21 years old Most of the lesions were yellowish red a few were bright red Many were covered with blood crusts Observed in Peru

stitutional symptoms disappear rapidly and the patient is on the road to recovery

The cutaneous lesions of the eruptive stage (Fig 55) present a picture which is unlike any other disease of the skin Some of the individual lesions closely resemble senile angiomas or pyogenic granulomas while others suggest generalized sarcomatosis However in its entirety the appearance of the eruption is unique The eruption consists of two distinct types of lesions (1) the so-called miliary or cutaneous type (Fig 55) and (2) the nodular or subcutaneous type (Fig 56)

The miliary type is much commoner and is more profuse than the nodular one (Fig 55) It is poorly named as only some of the lesions are the size of millet seeds and there is no resemblance whatever to the miliary papular syphilide or miliary tuberculosis of the skin The miliary type occurs most profusely on the extensor aspect of the extremities and to a less extent on the face and neck The palms and soles are usually spared and the genitals are only occasionally affected The term verruga (the Spanish equivalent of the Latin word verruca or wart) is a poor one as the majority of the lesions do not suggest warts either clinically or histologically The eruption begins as tiny papules which are said to arise on petechial spots They are hard at first but gradually become soft especially when they have obtained their maximum size that of a split pea Most of the lesions are discrete and of different size due to their appearance in crops Some of them disappear attaining

their maximum size The overlying skin is at first smooth but in the larger lesions it may be wrinkled and is often covered by black (hemorrhagic) crusts

The vascularity of the cutaneous lesions is shown by their tendency to bleed



Fig 56 Verruga peruana showing nodular type of eruption of three month duration on the hand of a girl aged 10 months A few lesions of the miliary type are present on the forearm Observed in Peru

on slight traumatism and by their redness Some of them are bright red while others are dull red or pink Itching may be present when the lesions are undergoing regression but in general itching is not a feature of the disease The eruption lasts from four to five months or more at times and disappears without leaving any trace

The nodular type of eruption (Fig 56) begins as shotty nodules in the subcutaneous tissue which can often be felt before they become visible The overlying skin may be normal in color or slightly red These lesions occur mostly on the extensor surfaces of the extremities A rare variety of the nodular type is called mula from the resemblance to a disease seen in mules These lesions occasionally become as large as a hen s egg or even a small apple and may be sessile or pedunculated When traumatized they bleed severely and may even cause death from hemorrhage

The mucous membranes as well as the skin may be the sites of the miliary type of eruption including those of the conjunctiva nose throat and gastrointestinal tract The nodular type however does not affect the mucous membranes

COMPLICATIONS AND SEQUELAE

When verruga peruana is complicated by the presence of other diseases such as malaria or paratyphoid B the prognosis is thought by some authorities to

be less favorable However in his experimental work with monkeys Noguchi found that both malaria and verruga could coexist without unfavorable effect of one disease upon the course of the other From his experience in a series of 36 cases of Oroya fever Ribeyro concluded that the coexistence of paratyphoid B made a fatal outcome most probable

The complete disappearance of the eruption is thought to be followed by permanent immunity with no sequelae In rare cases there may be a relapse of the eruption Odriozola referred to cases in which this occurred three and five years respectively after infection and in one case which Dr Edmundo Escomel related to me a mula type of lesion occurred on the great toe of a patient who had suffered from verruga eighteen years previously

DIAGNOSIS

While a possible diagnosis of the Oroya fever type may be made clinically it can only be made with certainty by demonstrating the *Bartonella* in smears or cultures The diagnosis of even a moderately profuse eruption of verruga can usually be made from its characteristic appearance One authority suggests that verruga may resemble the frambesiform eruption of secondary yaws The eruption of verruga does not remotely resemble that of yaws

PROGNOSIS

The prognosis of the Oroya fever type is always grave the mortality being perhaps 40 per cent on the average The prognosis of the verruga type is almost invariably good both as to life and the entire absence of any sequelae

TREATMENT

Many remedies including blood transfusions have been tried and found wanting Kikuth has recently (1937 and 1938) described a preparation of arsenic and antimony known as SDT 386 B which appears to have a specific action against *Bartonella* infection in rats He states that Manrique has obtained excellent results with this remedy in fourteen human cases of the Oroya fever type Others have failed to corroborate this work Ribeyro in 1940 stated that there was no specific treatment for the disease an opinion which is generally shared by the physicians of Peru

PROPHYLAXIS

Prophylaxis consists of remaining away from endemic regions after nightfall as the sandflies which transmit the disease are night flying insects If it is necessary to remain over night careful precautions should be taken against sand flies by the use of mosquito nets or screens

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SECTION FIVE

DISEASES CAUSED BY VIRUSES

CHAPTER XXXI

INTRODUCTION

ROSCOE R HYDE

THERE IS A LARGE GROUP OF DISEASES THE CAUSATIVE agents of which are not referable to the visible microscopic forms of parasitic life These maladies are widely distributed in nature and affect a wide range of plant and animal species They include many of our most destructive and rapidly spreading infections The inciting agents of this group of diseases have not been grown on lifeless media are not visible under the microscope and pass through filters that retain the banal type of bacteria Maladies produced by them are designated virus diseases and the causative agent is commonly referred to as a filterable virus

Among those viruses producing diseases in man may be mentioned small pox yellow fever dengue influenza poliomyelitis encephalomyelitis rabies varicella measles and mumps Among those producing diseases in animals are cowpox rabies foot and mouth disease rinderpest hog cholera fowlpox fowl paralysis encephalomyelitis of horses myxoma of rabbits wilt disease of the caterpillar and sac brood of the honey bee Among those producing diseases in plants are tobacco mosaic sugar cane mosaic, peach yellows and spindle tuber of the potato The list could be greatly extended for there are now approximately twenty known virus diseases of man one hundred of animals and some two hundred known virus diseases of plants with prospects of more coming to light Since so many of the domesticated varieties of plants and animals are affected by these maladies the viruses make serious inroads on the food and fiber supply of man They lay a challenge to man not only for his food clothing and shelter but for life itself The viruses accordingly present a problem of the first order of magnitude to those who would advance the cause of medicine

Until recently the virus diseases have been regarded as maladies of unknown etiology since they have not been identified microscopically or cultivated on lifeless media The assumptions have often been made that this group constitutes a sort of left-over assembly of unknowns and that when the causative agent in any given case is brought to light it will find its place among the visible well-defined forms of parasitic life Such assumptions are not warranted

It is no longer correct to speak of a true virus disease as a malady of unknown etiology The fact is that we know more of the behavior of some of these agents than we do of certain bacterial disease agents despite the fact that the latter can be seen and cultivated Facts are now at hand concerning a large number of virus diseases which show that the causative agents possess well defined characteristics that justify their inclusion in a separate and distinct group a group quite distinct from the bacterial the protozoon and other microscopic forms

(1) The causative agent is of a small order of magnitude as evidenced by the fact that it is not visible under the microscope and by the fact that it passes through filters that retain the microscopic forms of life

(2) The causative agent produces within certain cells of the affected host a well defined and characteristic pathology in terms of inclusion bodies

(3) The causative agent does not lend itself to cultivation on lifeless media

Not one of the agents possessing the first two of the foregoing characteristics has been cultivated in the bacteriologic meaning of that term Many of these agents however have been grown in cultures of living tissue For example when the filtrate from virus III of rabbits is added to a medium consisting of a balanced salt solution and blood plasma to which a fragment of rabbit testis has been added the virus readily multiplies and forms inclusion bodies which are easily demonstrated within the affected cells If however this fragment is first subjected to heat or to rapid freezing and thawing a process which kills the cells and is then added to the medium no multiplication of the virus takes place The viruses would seem to be so intimately bound up with the activity of living processes that they apparently can reproduce themselves only in some sort of intimate association with the living cells of a sensitive host

Bacteriologic methods fail at this point The viruses are not minute filter passing bacteria Bacterial forms beyond the range of microscopic vision have not been found despite the fact that several hundred different species of bacteria have been isolated Such isolations do not depend on size It would seem that the end point of microscopic resolution coincides with the lower limit of the degree of organization in which a living form can maintain itself as an individual with its own independent powers of metabolism on lifeless media

The virus diseases as a group may be arranged in a certain order in terms of the pathologic pictures which they produce At one end of the series are those diseases in which necrosis dominates the picture as in smallpox At the other end of the series are those in which hyperplasia and tumor like growths dominate as in the filterable tumors of rabbits and chickens Between these two extremes gradations appear This picture would seem to point to one of the most fundamental problems concerning these agents It is apparent that the cell is stimulated when it falls under the influence of the virus It may be stimulated to increase both in size and in number If the increase in size is the dominant force the cells balloon and finally break down giving rise to necrosis If on the other hand the cells increase in number perhaps at the expense of an

increase in size a tumor results If we knew all the links in the chain of the phenomenon that is here taking place we should no doubt be in a better position to bring some of these agents under control

A virus then as we conceive it at present is an agent of particulate nature It is of ultramicroscopic dimensions It passes through filters that retain the vegetative forms of parasitic life It can be passed in series on sensitive hosts In many cases it produces characteristic inclusion bodies It has not been cultivated and is most likely incapable of cultivation on lifeless media It apparently reproduces itself only in close association with living cells perhaps only within the living cell As an obligate cytotrophic agent it would seem to stimulate the cell to increase in size and in number The virus would be unknown to us were it not for the changes which it induces in living things that are more highly organized than itself We can neither deny nor affirm anything as to its animate nature It would appear in the light of the indications of its being protein in nature to be a transitional form spanning the distance from the dead to the living We now know the virus as the most destructive enemy of life itself and it becomes increasingly clear that the future well being of mankind is in no small measure dependent on the proper understanding of the ultimate nature and behavior of these agents

Recent advances indicate that the viruses may be characterized as definite *chemical substances In the case of tobacco mosaic* a highly *infectious disease* of the tobacco plant it is practically certain that the virus is an organic compound belonging to the class of heavy proteins Accordingly it would seem that we are at the threshold of gaining an insight into the identity and ultimate nature of these agents and with this will come a better understanding of their behavior It is to be expected that developments in this direction will contribute to a more intimate knowledge of the virus diseases with its consequent bearing on their prevention and treatment Considering the newness of the concept concerning the viruses and the necessity of recognizing and establishing them as a distinct group it is not strange that they have been known mainly through their effects Too little is yet known about the distribution of the viruses their level of infectivity their mode of transmission their portal of entry into the body and so forth Against the diseases resulting from them little except empirical measures is available for therapy even less for prophylaxis The viruses therefore are the principal causative agents of a group of diseases which are a constant medical concern

From the medical viewpoint our interest in the viruses is in terms of their behavior as parasites The problem of the parasite is to find a portal of entry to its host to travel to a favorable site and establish itself there to multiply and leave descendants to find an avenue of escape from one host and a pathway of entrance to a new host This usually involves many links in a long chain of events Our problem is to define the various links in this chain for any given parasite and to protect the host against disease by breaking the chain at some vulnerable point

The evidence in the following chapters on the various virus diseases will show that some of these links have been found and successfully broken We must continue to search for other links in the chain of events looking toward the elimination of the source of the virus or some easy and safe method of establishing a permanent immunity in the host

The minute size and intimate cytotropic properties of the viruses are important in their relation to the phenomenon of immunity The microscopic pathogens in general multiply on the surfaces and cavities throughout the body The host responds by the production of specific immune bodies which bring the invading antigen under the lytic action of alexin or sensitize it for the phagocyte It would seem that this mechanism is largely responsible for defending the individual against the invasion of bacterial agents

Since the viruses are proteins or are closely linked to proteins they act as expected as antigenic substances They stimulate the production of antibodies which may act at times in a manner similar to the humoral antibodies engendered by bacteria But the problem presented by the viruses is more complicated The viruses by virtue of their cytotropic tendencies house themselves inside the cell where they apparently multiply and exert their destructive *effects at times even in the presence of specific humoral antibodies*

The phenomenon may readily be demonstrated in tissue culture If a small fragment of testicular tissue from the rabbit is grown in vitro and if virus III is added a short time before the immune serum the formation of inclusion bodies shows that the virus multiplies and the cell is destroyed even though bathed in immune serum However if specific immune serum is added to the culture tissue a short time before the virus inclusion bodies fail to appear and the cell remains protected The cell apparently responds to the virus and immune serum on the principle of first come first served If a culture is made from the testicular tissue of an immune rabbit in normal serum inclusion bodies fail to appear when the virus is added The permanent and lasting immunity which in general characterizes the virus diseases must in ultimate analysis rest in the cell and active immunity in an individual must rest upon this changed state for after all the humoral antibodies are elaborated by the cells These antibodies may be used frequently with therapeutic success even to confer passive protection yet such immunity is at best only temporary

The foregoing facts fit the picture we find with the therapeutic use of immune serum in virus diseases For example there is little if any alleviation of paralysis in poliomyelitis following the injection of enormous quantities of immune serum Destruction of the nerve tissue has taken place before the disease manifests itself It is expecting too much of immune serum to think that it can restore damaged cells or that it can give more than slight help to parasitized cells Such treatment might however protect cells not yet invaded if such there be

It would appear at present that the therapeutic effects of immune bodies in the treatment of virus diseases are limited largely to the treatment of contact

exposures or early developing cases on the theory that they may in some way inactivate the virus on or before its anchorage and multiplication within the cell Such an assumption accounts for the effectiveness of convalescent serum in early cases of measles

The virus diseases as a rule confer a very solid and life long immunity So striking is this in the case of smallpox and yellow fever that it must have attracted attention long before the days of recorded history With the development of knowledge it became evident that the phenomenon was highly specific The immunity conferred by one disease afforded no protection against another disease The fact that a lasting immunity may follow a given infection has long inspired the hope that an immune stage could be produced without the necessity of the individual suffering from the malady Jenner demonstrated the first practical and safe way of doing this for smallpox Acting on the observation that milkmaids were immune to smallpox after contracting cowpox Jenner transferred pustular material from the affected cow to the arm of man by scarification A mild reaction resulted The principle was transferable on man in series It was an experimentally transmissible disease that did not spread by contact but that gave a lasting protection against smallpox Thus the process of vaccination was born and the conquest of the first virus disease was made possible

In order to establish anything like a lasting immunity in the host the presence of a living virus is required So universal have been our failures with the viruses inactivated by artificial means that we now question whether the immunity that results in rabies is not due to the active virus and that the virus is ineffective when it is actually killed

In the light of our failures with dead viruses as immunizing agents and in light of the solid immunity which can be induced with these active agents the question arises as to whether Jenner s prophylaxis is a law in itself After all may not the same basic principle underlie the immune behavior of other viruses? We now believe that Jenner did not use one disease to confer protection against another disease It is more in accord with the known facts to believe that cowpox is modified smallpox The smallpox virus has been changed by passage through this particular host so that it becomes relatively innocuous for man and renders him solidly immune to the fatal smallpox The cell of man acts on the principle of first come first served and if the modified virus reaches the cell first a mild reaction takes place which results in an enduring immunity

Pasteur fixed the street virus of rabies and attenuated it by drying Its virtue as an immunizing agent is usually ascribed to the process of attenuation In a sense Pasteur applied the Jennerian principle for it is the rabbit that changes the virus and renders it a relatively safe immunizing agent for man even when used in the fresh state In the case of yellow fever we now know that the virus is modified by passage through the brain of the mouse so that it becomes an effective vaccine for the prevention of yellow fever in man In the case of

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CHAPTER XXXII

YELLOW FEVER

FRED L SOPER

YELLOW FEVER IS A VIRUS DISEASE OF VERTEBRATES TRANSmitted by blood sucking invertebrates It occurs as a domestic and maritime human disease transmitted from man to man by the *Aedes (Stegomyia) aegypti* mosquito and as an infection of certain animals of tropical forests transmitted from animal to animal and accidentally to man by various species of mosquitoes and possibly by other arthropods

The etiology symptomatology immunology and pathology of jungle fever are identical with those of the *aegypti* transmitted disease but the epidemiology of one is quite different from that of the other

Yellow fever in man is a short self limited infection of variable severity having a single febrile paroxysm beginning three to six days after infection in classic cases followed by the symptoms of severe intoxication especially jaundice hemorrhage and anuria—the triad responsible for the terror that yellow fever universally inspires The virus of yellow fever is highly antigenic in man and non fatal attacks are followed by a lasting immunity The microscopic lesion found in the liver is characteristic and is not regularly simulated by that of any other acute epidemic disease

HISTORICAL NOTE

Yellow fever was unknown to the pre Columbian Mediterranean peoples and to Asiatic civilizations Europeans came in contact with the disease only after they began to penetrate in the fifteenth century the tropical lands of Africa and America bordering on the Atlantic Ocean The argument that the *Aedes (Stegomyia) aegypti* mosquito the only recognized vector of urban and maritime yellow fever is of Old World origin and that therefore the disease it transmits must be of similar origin loses its force in face of the demonstration during recent years that yellow fever exists in South American jungle forests as an animal disease independently of *aegypti* The Old World origin of *aegypti* and the conditions under which the American Indian lived suggest that yellow fever as a domestic urban or maritime disease was unknown before the arrival of the Spanish conquistadores and for some time thereafter since

fowlpox it is now believed that the virus is changed by passage through the pigeon so that the pigeon pox virus is an effective vaccine against the more virulent fowlpox

One means of controlling a deadly virus disease in terms of resistance would seem to be in terms of active immunity The principle underlying Jennerian prophylaxis would seem to have pointed the way Much success has been achieved with viruses modified by passage through appropriate hosts This is true for smallpox rabies yellow fever fowlpox and certain plant diseases

man mosquito man double cycle of infection was easily completed Had Finlay made these discoveries and demonstrated conclusively the mosquito transmission of yellow fever in the years following his publication of this theory Cuba might well have been made safe for Spanish troops and Panama for French canal diggers with important consequent alterations in the history of the Americas

All are familiar with the stories of Gorgas in Havana and Panama of Oswaldo Cruz in Rio de Janeiro and of others who armed with the secret of the transmission of yellow fever performed miracles in the broad light of day and became the prophets and saints of the public health movement overnight

Antimosquito campaigns in the important foci of yellow fever endemicity were followed by the disappearance of the disease not only from these foci but also from large tributary regions By 1915 only a few recognized endemic centers of yellow fever remained in the Americas including Guayaquil on the west coast and Baía and Pernambuco on the east coast of South America The *recently organized* Rockefeller Foundation *embarked on a program of collaboration* with the governments of the countries in which yellow fever might be found in an attempt to eradicate the disease completely from the Western Hemisphere Campaigns in the Central American countries Mexico Ecuador Peru Colombia and Venezuela were completely successful and by 1925 yellow fever was apparently limited in the Americas to a small coastal area of northeast Brazil where promising results were already being obtained

From the vantage point of 1943 it may be well to summarize the significant developments in yellow fever during the first quarter of a century following the demonstration of mosquito transmission in 1900

(1) The observation that yellow fever can be eradicated from a city by the single measure of reduction of *aegypti* breeding without screening or fumigating against adult mosquitoes and without attempting to control human population elements by isolation medical supervision and quarantine

( ) The demonstration that yellow fever would not long remain in the smaller towns and villages of the Gulf and Caribbean region of the Pacific coast of South America of the Amazon Valley and of south Brazil once the larger centers of population had been cleaned of the infection

(3) An improved description of the pathology of the liver in yellow fever with insistence on its specificity

It will be noted that no important etiologic laboratory development was registered for the period This was largely due to the danger of human inoculation and the failure to find a satisfactory animal host for the yellow fever virus lacking which many serious mistakes were made by highly qualified workers

In 1925 in anticipation of an early final victory in the Americas The Rockefeller Foundation organized a yellow fever commission for West Africa to determine whether the yellow fever of Africa was identical with that of the Americas and whether African conditions were favorable for a similar campaign of eradication This Commission succeeded in infecting various species dif monkeys with virus from human cases thus reopening the field of labor ins of

the introduction and dissemination of *aegypti* must have required a considerable period

The first clear description of yellow fever refers to an outbreak in 1648 which occurred appropriately enough in the Peninsula of Yucatan lying between the Gulf of Mexico and the Caribbean Sea The lands about these bodies of water came to be known during the following two centuries and a half as the principal endemic focus of yellow fever From this region yellow fever made with ever increasing frequency devastating summer excursions to the Atlantic and Gulf ports of the United States and to the Atlantic and western Mediterranean ports of southern Europe That the Yucatan outbreak was only part of a general Caribbean epidemic is suggested by accounts of epidemics of an unknown fever occurring in Barbados St Kitts Guadaloupe and Havana during the years from 1647 to 1649

Yellow fever apparently maintained itself in Cuba from 1649 to 1665 but disappeared from the records from 1666 to 1762 A similar behavior is recorded for northeast Brazil where following the first reported invasion in 1686 (Pernambuco and Bafa) yellow fever remained for a quarter of a century but was not seen from the early eighteenth century until 1849 The second invasions of Cuba in 1762 and of Brazil in 1849 found these countries with larger urban populations and increased commercial activity and permanent endemicity of *aegypti* transmitted yellow fever resulted in both Extension to the Pacific coast occurred as early as 1740 at Panama and Guayaquil both of which later became famous as permanent danger spots for the dissemination of yellow fever No country in the Americas has failed to pay tribute to this tropical scourge

Although Africa may have been the original home of yellow fever an unequivocal description of it there is not available before that of the 1778 epidemic among the British troops at St Louis de Senegal

Yellow fever in the Americas was a serious problem throughout the seventeenth century but in the nineteenth it became a most important economic and political factor Travelers to or through the American tropics paid a heavy toll and the movement of non immune troops through endemic regions often led to disaster Epidemics were no longer limited to the coastal ports but paralyzing outbreaks followed in the wake of rapid river and railroad travel as it developed in the interior

In 1900 yellow fever was rife in the American Army of Occupation in Havana Cuba although the city had been thoroughly cleaned by the Sanitary Service under Major Gorgas in the belief that yellow fever was a filth borne disease In the same year an Army Commission composed of Reed Carroll Lazear and Agramonte used human volunteers to study the theory of mosquito transmission so long advocated by Finlay The Commission discovered that when the *Aedes (Stegomyia) aegypti* mosquito was allowed to feed on patients within seventy two hours of onset of yellow fever and then kept during a ten to twelve day incubation period before feeding on non immune individuals transmissions of the infection occurred with regularity The man mosquito

man mosquito man double cycle of infection was easily completed Had Finlay made these discoveries and demonstrated conclusively the mosquito transmission of yellow fever in the years following his publication of this theory Cuba might well have been made safe for Spanish troops and Panama for French canal diggers with important consequent alterations in the history of the Americas

All are familiar with the stories of Gorgas in Havana and Panama of Oswaldo Cruz in Rio de Janeiro and of others who armed with the secret of the transmission of yellow fever performed miracles in the broad light of day and became the prophets and saints of the public health movement overnight

Antimosquito campaigns in the important foci of yellow fever endemicity were followed by the disappearance of the disease not only from these foci but also from large tributary regions By 1915 only a few recognized endemic centers of yellow fever remained in the Americas including Guayaquil on the west coast and Baía and Pernambuco on the east coast of South America The recently organized Rockefeller Foundation embarked on a program of collaboration with the governments of the countries in which yellow fever might be found in an attempt to eradicate the disease completely from the Western Hemisphere Campaigns in the Central American countries Mexico Ecuador Peru Colombia and Venezuela were completely successful and by 1925 yellow fever was apparently limited in the Americas to a small coastal area of northeast Brazil where promising results were already being obtained

From the vantage point of 1943 it may be well to summarize the significant developments in yellow fever during the first quarter of a century following the demonstration of mosquito transmission in 1900

(1) The observation that yellow fever can be eradicated from a city by the single measure of reduction of *aegypti* breeding without screening or fumigating against adult mosquitoes and without attempting to control human population elements by isolation medical supervision and quarantine

(2) The demonstration that yellow fever would not long remain in the smaller towns and villages of the Gulf and Caribbean region of the Pacific coast of South America of the Amazon Valley and of south Brazil once the larger centers of population had been cleaned of the infection

(3) An improved description of the pathology of the liver in yellow fever with insistence on its specificity

It will be noted that no important etiologic laboratory development was registered for the period This was largely due to the danger of human inoculation and the failure to find a satisfactory animal host for the yellow fever virus lacking which many serious mistakes were made by highly qualified workers

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ETIOLOGY

Yellow fever is the first human disease for which a virus origin was demonstrated This fact is often overlooked since the danger of human inoculation prevented extensive studies until after the discovery of a susceptible animal

Virus The virus of yellow fever is one of the smallest of the known pathogenic filterable viruses measuring between 17 and 28 millimicrons It is readily destroyed by temperatures about 55 C and by many chemicals and disinfectants Yellow fever virus may be preserved for several years if thoroughly desiccated in vacuum and stored at a low temperature but dies out rapidly if kept in serum or tissue at room temperature

The *A aegypti* mosquito once infected remains infective for life but infected laboratory colonies lose their capacity to infect exposed animals in about three months showing that there is no passage of virus from one generation to the next This is because the virus can not be passed through the egg stage of the mosquito Infective adult *aegypti* can be produced by exposure of the larval forms to large amounts of virus in blood serum or other liquid medium

Yellow fever virus has been cultured only in the presence of living cells Its growth is intracellular and cells in tissue culture once infected retain the virus and permit its multiplication even though immune serum be added to the medium

Yellow fever virus as isolated from human cases is said to be pantropic since it possesses *neurotropic* as well as *viscerotropic* properties Extraneural inoculation of pantropic virus in rhesus monkeys causes death with destruction of liver tissue whereas intracerebral inoculation in the white mouse which is insusceptible to visceral yellow fever is followed after a more or less prolonged incubation period by encephalitis By repeated passage under unfavorable conditions either in animals or in tissue culture it has been found possible to modify the tissue affinities of different strains of yellow fever virus Repeated mouse to mouse passages cause a reduction in viscerotropism and an increase in neurotropism virus so passaged loses its capacity to produce visceral yellow fever in man and monkey but acquires the power to kill mice after a shortened incubation period and produces fatal encephalitis with great regularity after intracerebral inoculation in monkeys Virus thus modified is used as the virus element in the mouse protection test

The modified strain (17D) now being used for vaccination has in the course of manipulation in the laboratory lost a great part of its neurotropism as well as its viscerotropism producing encephalitis in monkeys only occasionally after intracerebral inoculation and in mice only after an incubation period double that of the neurotropic virus

Differences in tissue affinity have been observed in different strains that have been isolated from human cases but these are slight in comparison with those produced in the laboratory No constant differences are found between *aegypti* transmitted and jungle strains of virus urban and jungle strains differing as much among themselves as they do from each other All strains of

investigation of yellow fever In the meantime the campaign for the eradication of yellow fever in the Americas failed in Brazil but in so doing it led to new discoveries in the epidemiology of the disease

From the same vantage *point* of *1913* but with of course a *poor* perspective for more recent events significant developments since 1925 may be summarized as follows

(1) The laboratory discovery that certain vertebrates other than man are susceptible to yellow fever and that mosquitoes other than *A aegypti* may transmit the virus from animal to animal

(2) The field discovery that yellow fever long considered to be a human domestic disease transmitted by a single vector is basically a jungle epizootic involving various vertebrate hosts and a number of mosquito vectors

(3) The epidemiologic observation that *aegypti* transmitted yellow fever does not necessarily disappear from surrounding areas after the reduction of *aegypti* breeding in the principal centers of population if (*a*) the rural sections of these areas are heavily infested with *A aegypti* (an unusual distribution of *aegypti* in northeast Brazil was found associated with a rural endemicity independent of reimportation of virus from urban centers) (*b*) the area is subject to reinfection by persons accidentally infected in the forests in the course of jungle epizootics (jungle yellow fever)

(4) The development of animal protection tests for immunity to yellow fever and their use to determine the previous exposure * of man to yellow fever virus in different parts of the world with the demonstration that the areas subject to yellow fever in both Africa and South America are greater than had been recognized

(5) The introduction of viscerotomy for the routine collection of liver tissues from persons dying after any febrile disease of short duration to determine the current presence or absence of fatal cases of yellow fever and the demonstration that (*a*) the yellow fever of silent endemic areas is not silent because of an absence of fatal cases in the native population but rather because of failure to recognize such cases (*b*) jungle yellow fever exists periodically throughout vast areas of South America from which the disease had never been reported

(6) The laboratory modification of yellow fever virus and the development of a safe and efficacious vaccine and the vaccination of several *million* persons in different parts of the world

(7) Development of a technique for the complete elimination of the *aegypti* mosquito from infested cities towns and rural areas and the organization of nation wide programs in various countries of South America based on permanent species eradication methods rather than the temporary mosquito reduction campaigns previously in vogue

* The youngest age at which immunity begins to appear in areas having a high *aegypti* density can be used as a measure of the interval which has elapsed between the last outbreak of yellow fever and the protection test survey but the same is not true in areas subject to jungle yellow fever since in many cases young children do not come into contact with the transnd thus escape infection until early adult life

The yellow fever of history was in great part the *aegypti* transmitted yellow fever of cities and ships although following the discovery of jungle yellow fever a number of references in the literature must have been found which

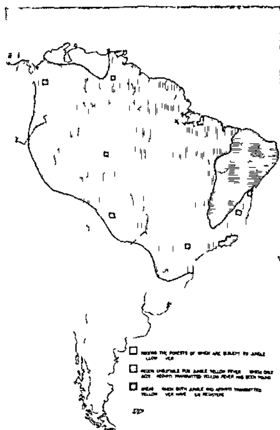


Fig 57 Distribution of yellow fever in South America based on epidemiologic studies and immunity survey 19 9–1941

indicate that this form of the disease is not new In fact there is good reason to believe that jungle yellow fever is the original epidemiologic type and that the *aegypti* transmitted variety is a relatively recent and exotic development

The *aegypti* mosquito is in the Americas at least essentially a domestic insect breeding in artificial water containers rot holes in trees and occasionally in rock holes along the streams close to towns and cities The proved vectors of jungle yellow fever *Aedes leucocelaenus* *Haemagogus capricorni* and an unidentified *Sabethine* breed in tree holes and in bromeliad and other parasitic plants above the ground in the tropical forests Another mosquito *Aedes scapularis* which is a ready transmitter of yellow fever in the laboratory is a grassy pool breeder This species is possibly responsible for man to-man trans

virus as isolated or as modified in the laboratory produce homologous antibodies in susceptible animals This specificity has been taken advantage of in the development of animal protection tests which have been used to determine the previous exposure of man and animals to yellow fever virus in different geographical areas The test is highly specific for the presence of antibodies in the blood of individuals of susceptible species but great care must be used in interpreting results from tests on species whose reaction to inoculation of virus has not been previously tested in the laboratory

In man yellow fever virus circulates in the peripheral blood stream in quantities sufficient to infect the *aegypti* mosquito only during the first three days of illness but may at times be demonstrated by the more sensitive animal inoculation methods as late as the fifth day at which time specific antibodies in the blood may already be demonstrable by the mouse protection test The behavior of vertebrates other than man following inoculation with yellow fever virus varies widely from that of the rhesus monkey which circulates the virus in high concentrations and produces large amounts of antibody to that of entirely resistant animals such as the canines in which no virus can be recovered from the blood stream nor can specific antibodies be demonstrated by the protection test

EPIDEMIOLOGY

In South America yellow fever has been described as

(*a*) *Aegypti* transmitted yellow fever occurring in the presence of this mosquito and disappearing when its density is reduced to a low level

(1) Urban yellow fever of cities towns and villages

(2) Endemic yellow fever of strictly rural areas

(*b*) Yellow fever without *aegypti* as

(*1*) *Jungle yellow fever* * *among individuals coming in direct* contact with the forest where the density and movement of the population is so low that human cases can be but incidental to an epizootic among jungle animals

(2) Rural yellow fever occurring under conditions suggesting a simple man vector man mechanism of transmission (very rare in South America)

* The use of the term jungle yellow fever has been criticized and the suggestion made that *the term selvatic or sylvatic yellow fever be used* as is done in describing rural plague However the terms selvatic and sylvatic have been used to refer to conditions that are merely rural or wild without respect to the type of vegetation cover present Jungle yellow fever as observed in various countries of South America always occurs in the presence of uncleared land and has not been observed in forests made up of a single type of tree The term jungle does not necessarily refer to the general type of cover in the area but to that at the particular place where the individual acquired his infection Outbreaks have been observed in prairie country in which the gallery forests along the water courses represented only 5 per cent of the total terrain and in previously heavily forested areas in which but a small part of the land remained uncleared Under these conditions cases have occurred only among those who have gone into the forest to cut timber to hunt or to fish to fetch water or to wash clothes at a stream flanked by jungle cases often being limited to one in a family

that young adult males are more susceptible than are other groups In the native population of highly endemic regions yellow fever is almost entirely limited to young children in whom the disease even in fatal cases is often difficult to diagnose



Fig 58 Localities in which recognized outbreaks of yellow fever have occurred

Jungle yellow fever is generally acquired by direct contact with the forest or with the margin of the forest and is a house disease only when the house itself stands in the forest Daytime infection of human beings is most frequent In areas where contact with the forest is limited to lumbermen and hunters almost all of the cases will be in young adult males whereas in districts where the field work such as coffee picking is light often entire families will spend many hours a day where exposure is easy with the result that men women and children are attacked Even so it is very unusual to find so thorough an immunization of the native population as occurs in endemic centers subject to

fer in rural areas and even for jungle yellow fever in flat forest regions.

In South America a sufficiently widespread distribution of *A. aegypti* to permit of rural endemic yellow fever has been found only in a section of northeast Brazil where a semiarid climate and occasional severe droughts necessitating the storage and transportation of water by travelers have greatly facilitated the spread of *A. aegypti* in rural areas.

In South America no important series of cases of rural yellow fever without *aegypti* have been observed away from rather close contact with the forest, and the few cases in which history of such contact could not be established were in intimate relation with areas of jungle yellow fever activity.

Aegypti-transmitted yellow fever is essentially an epidemic disease which depends on an unbroken series of cases at relatively short intervals, since the vertebrate element concerned, man, is infective for mosquitoes for only a few days, rapidly becomes permanently immune, and is never a carrier, and the invertebrate element, the *aegypti* mosquito, is a short-lived insect which does not pass the infection from one generation to the next through the egg. Local urban endemicity occurs only where there is a constant supply of non-immunes and an adequate density throughout the year of the *A. aegypti* mosquito. Regional and rural endemicity is maintained through a series of small epidemics in one community after another, outbreaks flaring up after a fresh supply of non-immunes has accumulated, through birth or immigration, between successive visitations to any one community.

Yellow fever disappears from an urban center within six or seven weeks after the reduction of the breeding foci of the *aegypti* mosquito to a low level, showing that the effective period of virus preservation by *aegypti* in nature is only about half as long as that registered for protected laboratory colonies. In small communities with high density of *aegypti*, but with little or no immigration of non-immunes, yellow fever spontaneously disappears after a few months.

Apparently similar factors are involved in the story of jungle yellow fever. There seem to be certain permanent enzootic areas where jungle yellow fever, as revealed by occasional human cases, persists indefinitely, probably, drawing an analogy from endemic *aegypti*-transmitted yellow fever, because of a high density of susceptible animals of short-lived species among which immune adults are frequently replaced by non-immune young. Other regions suffer occasional epizootics lasting two to three months, during which the forests are dangerous to human visitors, with intervals of three to ten years when no evidence of the disease is found. In this case, yellow fever apparently disappears because of an exhaustion of non-immune animal hosts rather than of susceptible human beings.

Aegypti-transmitted yellow fever is essentially a house disease, and non-immune persons of all races, ages, sexes, and occupations who come to the infected house are liable to infection. The tendency of non-immune immigrant groups consisting mostly of young men to crowd into the poorer district of a city where the *A. aegypti* infestation is often extreme gives the impression

on which these depend are due to mosquito transmission of virus No explanation is offered of the mechanism whereby the virus of yellow fever over winters in the forests of central and south Brazil where neither human cases nor evidence of epizootics can be found during several months of the year

Geographical Clinical yellow fever has not been recognized anywhere in North America Central America the West Indies Europe and the Mediterranean region since 1925 Protection test surveys tend to confirm the absence of yellow fever from these regions previously subject to yellow fever with the single exception of Panama where several positive tests have been found in persons born since that year

In South America on the other hand there is reason to believe that only Uruguay and Chile have completely escaped during the same period *Aegypti* transmitted outbreaks have been registered for Colombia Venezuela Bolivia and Brazil and jungle outbreaks for Colombia Venezuela British Guiana Brazil Peru Paraguay and Bolivia Suggestive protection test results are available for Dutch and French Guiana and from the province of Missiones in Argentina

Aegypti transmitted yellow fever secondary to immediately preceding jungle yellow fever has been observed as recently as 1937 but *aegypti* transmitted outbreaks depending upon previous *aegypti* transmitted yellow fever for infection have not been observed on the continent since 1934

In Africa yellow fever has been shown by protection test surveys to extend much farther inland than was previously recognized An outbreak of some 15 000 cases in the Anglo Egyptian Sudan in 1940 was the first large-scale confirmation of these surveys This was followed by isolation of yellow fever virus in Uganda in 1941 In East Africa and in Asia however yellow fever has never been found

PATHOLOGY

The gross appearance of the body after death from yellow fever is characterized by congestion hemorrhage and jaundice in varying combinations Immediately after death the congestion may mask the jaundice whereas a few hours later the settling of the blood to the more dependent parts of the body makes the jaundice more apparent Jaundice may be slight in fulminant cases but will generally be found on examination of the ocular conjunctivae and mucosa of the palate External evidence of hemorrhage is often found about the nasopharynx lips and gingivae and sometimes subcutaneously or intramuscularly Internally jaundice is noted in the subcutaneous fat and in the walls of the aorta and other arteries

The liver is generally normal in size a pale yellowish color and of a fatty consistency The heart is pale and flabby the kidneys tense and swollen Evidence of hemorrhage may be found in any of the organs or serous surfaces but is especially common in the stomach and intestines where partially digested blood (black vomit) is often observed

The most important lesions found in yellow fever from the standpoint of

aegypti transmitted yellow fever with the result that jungle yellow fever always tends to give a high percentage of adult cases

Aegypti transmitted yellow fever spreads along the routes of human travel



FIG 59 Areas of yellow fever in Africa

and is generally carried by the human passenger more rarely by the infected mosquito Jungle yellow fever on the other hand moves through the forest areas without respect to human routes of travel the apparent rate of spread being at times so great as to suggest dissemination by birds

The spread of *aegypti* transmitted yellow fever often depends on the movement of mild cases which are not diagnosable even in the course of a recognized epidemic. Likewise the cebus monkey which circulates virus in the blood stream but which does not die of yellow fever is because of its greater numbers probably much more important in the spread of the disease than is the howler monkey which often succumbs to infection

SEASONAL AND GEOGRAPHICAL DISTRIBUTION OF YELLOW FEVER

Seasonal Both urban and jungle yellow fever may occur in the tropics at all seasons of the year but tend to have their greatest incidence during the rainy season In more temperate climates human cases of both varieties of yellow fever are largely limited to the summer and fall months Field studies indicate that jungle yellow fever cases and almost certainly the summer epizootics

bloody vomit hypoglycemia depression prostration and death with autopsy showing hemorrhagic areas at the pyloric end of the stomach and in the duodenum The similarity of this picture to that of yellow fever is marked

SYMPTOMATOLOGY

Clinically yellow fever is a self limited infection of a single paroxysm of one to three rarely four days duration followed in severe cases by a self limited intoxication lasting up to seven or eight days

Yellow fever cases vary clinically as much as do those of measles smallpox poliomyelitis and other virus diseases Yellow fever occurs as

(1) Inapparent infection which fails to register in the memory of the victim and which is recognized only through the demonstration of acquired immunity

(2) Influenza like infection without coryza lasting only some hours or possibly two or three days in which the diagnosis may be suggested by an unexpected albuminuria and by bradycardia during convalescence This is probably the most common clinical type of yellow fever

(3) Severe infection with sudden onset high fever headache backache leg pains and temperature and pulse curves typical of yellow fever but without the succeeding symptoms of intoxication namely hemorrhage jaundice oliguria and anuria Albuminuria and cylindruria may suddenly appear and rapidly increase on the third fourth or even fifth day in the absence of other severe symptoms

(4) Classic yellow fever in which following a typical onset with symptoms of severe infection there occur during the second stage albuminuria oliguria hemorrhage (black vomit) and jaundice The classic case may be mild in character if the hemorrhage is not excessive and the kidneys continue to secrete Marked oliguria and anuria are found only in cases with hemorrhage and jaundice

The early phase of yellow fever is marked by the usual signs and symptoms of acute infection but there is nothing to suggest the overwhelming intoxication which may supervene as the infection itself declines The classic clinical picture of yellow fever is that of the second phase which is one of intoxication rather than infection and consists of a symptom complex associated with the loss of hepatic and renal function which is common to a number of diseases and intoxications involving destruction of liver parenchyma This complex is not in itself pathognomonic for yellow fever but the definite sequence of symptoms creates a specific clinical entity which is very characteristic

Period of Infection The onset of yellow fever is rapid and the exact hour of attack can generally be given by the victim whose initial subjective symptoms headache backache pain in the legs and prostration are out of all proportion to the physical findings Examination reveals evidence of a general superficial congestion of conjunctivae skin and mucous membranes an increased pulse rate up to 1 o per minute and body temperature generally 38 to 39 , C

explaining the symptoms of intoxication and of making a definite postmortem diagnosis are those revealed by microscopic examination of the liver Lesions are found in the kidneys heart and spleen but their importance is completely overshadowed by those of the liver

The liver section of a typical yellow fever case shows much fatty degeneration and a varying amount of parenchymal necrosis with no evidence of inflammation or of connective tissue proliferation There is a jumbling of the trabeculae which is more accentuated in the midzone of the lobule Fatty degeneration is a constant feature although the size of the globules found and their number may vary greatly Fat globules are generally more pronounced in the parenchymal cells of the peripheral and central zones of the lobule than in those of the midzone where the necrosis is more evident The necrosis of the parenchyma in yellow fever may involve few or almost all of the cells but its distribution is always of a salt and pepper rather than focal or massive type The greatest concentration of necrotic cells is in the midzone of the lobule and the necrosis of the cells about the periphery and about the central vein is never complete

Experience has shown that regeneration of the yellow fever liver begins very early in convalescence and may be well advanced in patients dying from complications during convalescence However although the appearance of the liver changes greatly it is possible to follow the devolution of the Councilman bodies and make a diagnosis on their appearance and distribution as late as three weeks after onset

Studies on the rhesus monkey infected with yellow fever show that there are but slight changes in the chemical components of the blood serum during the first stage but that shortly before death important alterations are found of a type usually correlated with extensive destruction of liver tissue Only if yellow fever has produced obvious symptoms of intoxication do the concentrations of the nitrogenous constituents of the blood become appreciably altered The most significant change is that in the amino-acid nitrogen which shows strikingly large gains both in absolute amount and in relation to total nitrogen The changes noted indicate a loss of ability to deaminize amino acids and to form urea a deficiency of uric acid production and an impairment of hepatic glycogen formation all of which are found following hepatectomy It is difficult to escape the conclusion that they are dependent on the destruction of liver parenchyma

Extreme hypoglycemia may occur without hyperuricacidemia Hypoglycemia is a common finding in human intoxications of yellow fever A significant increase of blood guanidine has been found in monkeys and a similar finding has been reported for a human case A similar increase of guanidine in the blood has been found in other diseases and intoxications in which extensive liver damage occurs such as carbon tetrachloride phosphorus arsphenamine chromium and chloroform poisoning and acute yellow atrophy Laennec's cirrhosis of the liver and eclampsia Guanidine poisoning in dogs produces

hemorrhage of yellow fever is that of the second phase Serious hemorrhage generally develops somewhat later than does albuminuria although in fulminant cases second phase hemorrhage may begin as early as the end of the second day Hemorrhage may be so severe as practically to exsanguinate the patient and is undoubtedly often the immediate cause of death When present hemorrhage is a much more striking feature of yellow fever than is jaundice and fully justifies the Spanish in calling the disease *vomito prieto*

Albuminuria The onset of albuminuria is rapid as if some sudden violent intoxication involving renal function had occurred rather early in the course of the infection A sudden and progressive increase in the albumin content of the urine with elimination of hyalin and granular casts occurring as early as the end of the second day or as late as the fourth or even fifth day of illness is one of the most common findings in yellow fever Practically all except very mild transient cases show a much heavier albuminuria than would be expected in severe fevers due to other causes Heavy albuminuria may be found in cases showing no other symptoms and is not in and of itself of serious prognosis

Anuria Anuria is the most dreaded symptom of yellow fever and it may occur unexpectedly in patients having an otherwise favorable prognosis Anuria apparently depends on an entirely different mechanism from that producing precocious albuminuria The former is never found in cases without other signs of liver destruction whereas the latter may be heavy in mild cases without such signs Anuria follows and seems to depend on liver involvement albuminuria may precede and even be independent of other signs of hepatic intoxication It is probably safe to conclude that albuminuria may occur either as a result of direct involvement of renal function during the infection phase or later because of intoxication secondary to destruction of hepatic parenchyma but that anuria is produced only by this secondary intoxication

COMPLICATIONS AND SEQUELAE

Relapses or repetitions of the original onslaught of yellow fever have not been confirmed by laboratory methods for man or monkey There is also strong reason to believe that the period of intoxication is a definitely self limited phenomenon generally lasting not more than a week In cases in which an apparent relapse of this period of intoxication is observed after the tenth day of illness an autopsy may be expected to show some cause of death other than yellow fever

Cases with severe symptoms of liver involvement during the period of intoxication often show a lowered resistance to secondary infection which may develop about the time of convalescence Abscesses especially of the kidney pneumonia unilateral parotitis multiple skin infections and even gangrene may occur Death from these secondary causes may occur as late as three weeks after the onset

Convalescence Convalescence from the symptoms of intoxication is rapid and complete except for a longer asthenia probably due to heart muscle changes the electrocardiograph showing that heart action may not return to

(100 4 to 103 1 F) rarely higher the blood pressure is normal or slightly increased whereas the white blood cell count begins to drop on the first day and a leukopenia is the rule during the first five or six days of the disease The abdomen is generally flat and without signs of local tenderness except over the left hepatic lobe

The infection is often explosive in character the pulse and temperature reach their fastigia on the first day after which there is a tendency for both to decline the pulse falling sooner more rapidly and more constantly than does the temperature (Faget s sign)

Nausea and bilious vomiting are often found during the period of infection Incidental hemorrhage associated with the congestion such as epistaxis, may occur and is responsible for any blood streaked vomit of this period

Generally at the end of the first forty-eight to seventy two hours the congestion declines the temperature reaches normal or even subnormal levels and the patient loses his restlessness and enters a period of relative tranquility which marks the end of the period of infection This period of calm is often the beginning of frank convalescence but in severe cases it is but a stage of transition lasting a few hours or a full day leading to the period of intoxication

Period of Intoxication About the end of the third day but sometimes as late as the fifth the entire clinical picture changes The active congestion of the previous period is replaced by a venous congestion accompanied by low arterial tension and often an extreme bradycardia develops and persists in spite of a secondary rise in temperature nausea and vomiting which may have been present during the period of infection are now more severe are associated with epigastric pain and are of grave import Overwhelming intoxication becomes apparent with the appearance of albuminuria hemorrhage (black vomit melena) jaundice oliguria and anuria In fulminant cases symptoms of intoxication are precocious and merge with those of the phase of infection

It should be noted that not only are the symptoms of the second stage those of intoxication but that there is a rapid disappearance of virus from the body beginning toward the end of the third day and that as early as the fourth day there is a demonstrable amount of antibody present in spite of which the symptoms of the second stage occur and may progress to a fatal termination

Jaundice The jaundice of yellow fever may be so slight as to be missed by the inexperienced and is rarely or never intense in early cases Subicterus is the most common finding and may be noted in the conjunctivae as early as the end of the second day but marked visible cutaneous icterus appears late and is often not noted ante mortem in fulminant cases in which symptoms of intoxication appear before those of infection have abated Evidence of jaundice is practically always found at autopsy

Hemorrhage The amount of hemorrhage noted in yellow fever cases varies greatly but some tendency to hemorrhage is to be found in the majority of clinically diagnosable cases Although slight hemorrhage may and often does occur during the initial stage of active congestion the dangerous typical

(5) *Hemorrhage* Epistaxis and oozing of blood from gums may appear early but the typical hemorrhage of yellow fever black vomit melena cutaneous hemorrhage and more rarely hematuria are second stage manifestations oc curring generally not before the fourth day Bright red blood may be vomited early or late

(6) *Initial Congestion* Begins on first day and involves ocular conjunctivae oral mucosa and skin giving dusky appearance to ears and chest of white patients

(7) *Initial Headache* Severe headache is a constant finding

(8) *Patient s Story* Subjective symptoms are severe

LABORATORY DIAGNOSTIC PROCEDURES

Special laboratory procedures have come to be indispensable in the confirma tion of a diagnosis of yellow fever in suspect cases but even more so for calling attention to the existence of suspect cases in a given region Although comple ment fixation and precipitin tests could be used the following three laboratory methods are the most reliable and widely employed for establishing a diagnosis in suspect cases

(1) Isolation of virus in susceptible animals

( ) The double animal protection test initial negative test followed by positive test beginning the fifth day after onset

(3) Microscopic examination of liver tissue removed po t mortem Cases have been recorded in which confirmation was made by all three methods

Isolation of Virus Blood from early febrile cases (preferably obtained dur ing the first three days although positive results have been secured up to the fifth day) is infective for animals In the field patients may be bled into venules and these placed directly in thermos bottles with ice and salt mixture for transfer to the laboratory for animal inoculation Under these conditions the virus easily resists almost any amount of travel Since mice are small easily transported and do not circulate virus in the peripheral blood stream after the second day postinoculation they may be taken to the field for inoculations Monkeys should be inoculated only under conditions which permit of care ful control of the animals in well screened cages since virus may circulate early and infect mosquitoes en route to the laboratory Work with virus should not be undertaken by non immunes as witness the cases of Stokes Young Noguchi Lewis and Hayne as well as a larger number of non fatal cases oc curring in the years immediately following the first successful animal inocula tions before vaccination methods became available

Rhesus monkeys after intraperitoneal or subcutaneous inoculation may be come febrile as early as the third day after inoculation and death may occur as early as the fourth day with typical lesions in the liver White mice inocu lated intracerebrally may begin to show paralytic evidence of encephalitis as early as the seventh day but often remain well until somewhat later and in cases where little virus has been present in the inoculum the first appearance

normal for many months Even in very mild cases asthenia of five to ten days duration is common Permanent damage to liver or kidneys from yellow fever is not apparent

CLINICAL DIAGNOSIS

The clinical diagnosis of yellow fever in spite of the striking picture of the classic case may be difficult in the individual case in the absence of a declared outbreak The clinical picture at any given moment may be simulated by other infections and intoxications but the sequence of symptoms is generally distinctive An initial period with symptoms of acute infection with sudden onset with the signs of active congestion and with subjective symptoms of restlessness and prostration out of all proportion to the physical findings followed after two to four days either with or without an intervening period of calm by a period in which symptoms of severe intoxication dominate the picture leaves little doubt as to the diagnosis of yellow fever Points of special interest in the observation of the patient include

(1) *Tongue* Has clean red margins and pointed tip throughout the illness in contrast with upper surface which may become progressively white-coated brown coated and clean red in appearance

(2) *Albuminuria* Increases rapidly and progressively beginning as early as the second or as late as the fifth day more intense than the albuminuria found in other acute infectious diseases

(3) *Jaundice* Jaundice is not an initial symptom of yellow fever is not usually intense and is often absent from mild cases It is often first noted in the conjunctivae where its combination with the preceding congestion produces a picture similar to that of the egg yolk and the vitelline vessels of the five or six day old chick embryo All degrees of cutaneous jaundice are found from slight to intense The disease was apparently named from the appearance of very severe or fatal cases in the white race

(4) *Pulse and Temperature* Although the behavior of pulse and temperature is not constant and is undoubtedly influenced by such factors as transportation of the patient by the degree of restlessness and by the type of medication administered careful study of the relationship of these two elements is important Both pulse and temperature tend to reach their highest reading some hours after onset with the pulse beginning to drop in most cases as early as the second day and the temperature soon thereafter The secondary rise in temperature which may occur during the period of intoxication often has no influence on the pulse rate which continues its downward trend in most uncomplicated cases except *in extremis* The pulse is generally slow after the third day in yellow fever and a pulse of more than 100 beats during the second stage suggests severe hemorrhage secondary infection impending demise or that the case is not yellow fever Bradycardia is the rule and may become extreme pulse rates as low as 40 per minute being not uncommon Bradycardia often continues into convalescence

methods of fixation and staining fixation in 10 per cent formalin and routine staining with hematoxylin and eosin are entirely satisfactory in spite of the insistence of some pathologists on special methods

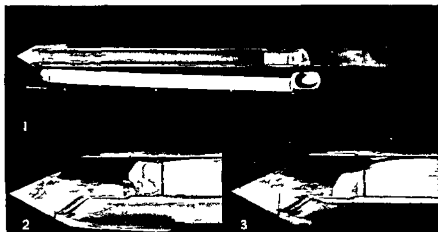


FIG 60 Viscerotome 1 Instrument with slide or blade removed 2 Enlargement to show position of distal end of sliding blade when instrument is open 3 Enlargement to show position of sliding blade when instrument is closed

While it is true that certain other conditions may produce a liver lesion similar to that of yellow fever and that fatal burns may even duplicate it experience has shown that yellow fever is the only acute infectious disease in which this lesion is regularly found The lesion is a complex one the characteristic feature of which is not the simple presence or absence of a special type of necrosis but rather the salt and pepper distribution of this necrosis throughout the lobule with the greatest frequency in the midzone of the lobule in combination with other changes The liver of the carbon tetrachloride poisoning case in which destruction of the parenchyma has not been massive may show a salt and pepper distribution of necrosis throughout the lobule but with the greatest frequency in the central zone Otherwise the lesion is very similar to that of yellow fever

Occasionally other severe infections (peritonitis pneumococcic meningitis etc) and intoxications (fuadin) may produce lesions similar to those of yellow fever but these can generally be eliminated by careful history taking

Advantage has been taken of the specificity of the yellow fever lesion in the liver to organize viscerotomy (Fig 60) for determining the presence of yellow fever in endemic and epidemic regions in the complete absence of reported suspect cases To be fully effective viscerotomy must be routine over a long period and must operate without regard to the presence or absence of declared suspect cases For efficiency in the discovery of jungle yellow fever viscerotomy must operate in small isolated communities incapable of maintaining practic

of encephalitis may be as late as the end of the third week after inoculation

Virus other than that of yellow fever may produce encephalitis in mice but experienced workers are generally able to say whether or not a given group of animals has been infected with yellow fever virus without waiting for the results of specificity tests

Double Protection Test The double protection test may be used to establish a diagnosis in suspect cases seen during the first few days after onset or may be used to survey a given population at intervals

The protection test is based on the observation that the intraperitoneal inoculation of a mixture of neurotropic yellow fever virus and normal serum in a highly susceptible strain of white mice such as the so-called Swiss strain in which intracerebral irritation has been set up by intracranial inoculation of starch causes a fatal encephalitis in most of the animals so inoculated whereas a similar inoculation of a mixture of neurotropic virus and serum from a person or animal known to be immune to yellow fever protects most of the animals

The virus element for the inoculation of mice in the protection test is prepared by removing pooling triturating and emulsifying in physiologic saline solution the brains of a number of mice inoculated intracerebrally with neurotropic virus *three or four days before the test is to be run*

When adult animals are used for the test these should be inoculated intracerebrally shortly before the test with 0 03 cc of a 2 per cent starch solution If young mice nineteen to twenty one days of age are used this step is unnecessary

For the adult mouse test 3 0 cc of the serum to be tested is added to a tube containing 1 5 cc of virus emulsion and each of a group of six test animals is inoculated intraperitoneally with 0 6 cc of the mixture With young mice satisfactory results are obtained using only 0 1 cc of serum and 0 2 cc of virus emulsion each animal being inoculated with but 0 06 cc of the mixture Adequate controls containing normal serum dilutions of immune serum and various dilutions of virus emulsion are set up for each run

In the absence of specific antibody mice begin to sicken on the fourth day and may all be dead by the sixth day Evidence of antibody may range from complete protection of all animals against encephalitis to a mere lengthening of the survival time The serum of persons having suffered from a recent attack of yellow fever may be expected to prevent death in *all* or *in at least* five out of six of the test animals inoculated

The protection test is apparently always clearly negative during the first three days after onset may be doubtful on the fourth day and clearly positive as early as the fifth day The double protection test used in epidemiologic surveys establishes the fact that negatives on one test found positive on subsequent test have been exposed to yellow fever virus during the interval between these tests

Microscopic Examination of Liver Tissue Fortunately the examination of sections of liver tissue for the lesions of yellow fever does not require special

and hemorrhage may be important features. Influenza cases often show coryza and have much less congestion, vomiting and albuminuria than do those of yellow fever.

(2) *Malaria.* Malaria may coexist with yellow fever either as acute or chronic infection. Malaria simulating yellow fever may occur in primary infections with *P. falciparum* or in chronic cases of *P. vivax* infection.

(3) *Blackwater Fever.* Jaundice and hemoglobinuria appear very early, whereas in yellow fever hemoglobinuria is rare and does not appear before the third or fourth day.

(4) *Epidemic Jaundice.* There is absence of the severe symptoms of onset found in yellow fever. Absence of congestion gives jaundice yellow or yellow-green tinge in conjunctivae. The disease is generally more prolonged and the jaundice is often intense in comparison with other symptoms, which may be mild.

(5) *Weil's Disease.* There is absence of initial congestion. Early leukocytosis occurs. The course of disease is slower than that of yellow fever. Blood examination and guinea pig inoculation for isolation of organism may be made up to the sixth day; thereafter urine should be used for guinea pig inoculation.

(6) *Smallpox.* The type and severity of the early symptoms are very suggestive of yellow fever. Differentiation may be difficult during the first three days of the disease before characteristic cutaneous lesions of smallpox appear. Should diagnosis not be made during life and the liver be sent in for examination, the finding of necrosis may cause suspicion of yellow fever among those not fully familiar with the yellow fever liver.

(7) *Dengue.* Clinically dengue is very similar to mild yellow fever. The appearance of the rash is the most useful distinguishing sign. The absence of fatal cases is often significant.

(8) *Rickettsial Disease.* Sao Paulo typhus (Rocky Mountain spotted fever) occurs in the winter rather than in the summer months in south Brazil. Rapid pulse, body rash, and so forth are distinguishing features.

(9) *Plague.* The presence of bubo from which bipolar bacilli can be isolated by guinea pig inoculation serves to differentiate plague from yellow fever.

(10) *Relapsing Fever.* Leukocytosis, spirochetes found by darkfield examination or by animal inoculation, rapid pulse are distinctive for relapsing fever.

(11) *Carbon Tetrachloride Poisoning.* The onset follows anthelmintic medication. There is absence of congestion and typical symptoms of infection. The pulse and temperature curves are not those of yellow fever. The final stage of carbon tetrachloride poisoning may resemble grossly that of yellow fever. Salt and pepper necrosis of the liver is central, not midzonal, in distribution.

(12) *Meningitis.* Neck rigidity, Kernig's sign, leukocytosis and the presence of the organisms in turbid cerebrospinal fluid are the signs diagnostic of meningitis.

ing physicians The routine adopted in South America calls for viscerotomy service to have a local representative under contract paid on piece work basis according to the number of liver specimens sent in The viscerotomist is responsible for ascertaining the duration of illness in fatal febrile cases occurring in his area and obtaining with the viscerotome liver tissue from the bodies of all persons over one year of age dying after less than eleven days illness Viscerotomy has repeatedly given the first information of the existence of yellow fever even in communities in which the cases diagnosed thereby had had medical attention

Epidemiologic Observations Epidemiologic observations are often very important in pointing to a diagnosis of yellow fever In highly endemic areas of *aegypti* transmitted yellow fever in the absence of viscerotomy classic clinical cases will be limited almost entirely to newly arrived adults from non endemic regions In tropical regions jungle fever may occur at any time of the year but in temperate climates is largely limited to the summer months and attacks only those who work in contact with the forest itself Rumors of black typhus and of fevers carrying the names of the places where they occur should all be investigated as suggestive of jungle yellow fever Reports of visceral malaria of malaria without parasites of malaria of uninhabited forests and of malaria resistant to quinine will often lead the investigator to jungle fever

DIFFERENTIAL DIAGNOSIS

Some or all of the symptoms of the first stage of yellow fever may be duplicated by other acute infectious diseases and those of the second stage may occur in individual cases of other diseases in which especially severe signs of intoxication are present Too much emphasis cannot be placed on the importance of subjective symptoms and the course of the disease after onset in all suspect cases of yellow fever

Among the recorded mistaken clinical diagnoses are influenza malaria blackwater fever epidemic jaundice acute nephritis and strangulated hernia for yellow fever and yellow fever for Weil s disease smallpox measles dysentery dengue rickettsial disease pneumonia plague meningitis relapsing fever carbon tetrachloride poisoning and scurvy In Africa kukuruku disease Rift Valley fever Bwamba fever and West Nile virus disease exist within the regions subject to yellow fever outbreaks

(1) *Influenza* It is sincerely to be hoped that the recent development of methods for the isolation of influenza viruses in animals and of methods for determining variations in immunity to them will eventually take the group of infections classified under the term influenza out of the category of a catchall diagnosis for all febrile diseases of unknown etiology However there has been some excuse for confusing influenza and yellow fever since the symptoms of onset are superficially similar in the two diseases and the gross picture at death in yellow fever is not unlike that of epidemic influenza cases in which jaundice

is it possible to understand the past acceptance and popularity of many forms of treatment for yellow fever since abandoned Once yellow fever has declared itself there are no known specific serologic or chemical therapeutic agents of value

The inoculation of small amounts of immune serum just before together with or within a few hours after the inoculation of yellow fever virus in rhesus monkeys is effective in preventing infection but with the use of such serum even in large amounts after onset of symptoms in either man or monkey the course of the disease is not appreciably altered

Apparently the onset of symptoms in yellow fever occurs only after the virus is widely distributed and safely entrenched intracellularly throughout the body

The results of chemical analysis of the blood would seem to indicate the use of glucose to combat hypoglycemia and of calcium salts to neutralize the guanidine like toxins common to conditions causing destruction of liver parenchyma *The use of calcium lactate and glucose so successful in some other in*toxications has not been followed by recovery of monkeys showing signs of intoxication nor have striking results in man been demonstrated

Symptomatic Treatment Although there is no specific treatment of yellow fever there are certain clear indications for careful handling of all cases even apparently mild ones

To meet the involvement of the circulatory system which occurs early is often severe and may persist far into convalescence the patient should not be moved from the place of attack especially after the first day Activity during convalescence should be resumed very gradually Careful nursing is essential

The gastro-intestinal tract should be relieved of its routine responsibilities An initial saline purge may be given on the first day followed by daily enemata Abstinence from food except fruit juices to combat hypoglycemia should be absolute during the infection phase and until after the temperature has returned to normal in the intoxication phase Water Vichy water or water alkalinized with sodium bicarbonate and citrous fruit juices may be given frequently in small amounts If vomiting prevents taking liquids by mouth recourse may be had to intravenous dextrose normal saline by hypodermoclysis and tap water by rectum For direct relief of vomiting cracked ice and cocaine hydrochloride 0 015 gm (¼ grain) U S P may be given by mouth and codeine sulphate 0 03 gm (½ grain) U S P by hypodermic injection Feeding should be resumed slowly beginning with chicken broth buttermilk rice water crumbled egg yolk and easily digestible liquids with added lactose

High temperature may be relieved by an ice cap to the head and by te id sponge baths Depressant antipyretic drugs should not be used I where yellow fever may be present it is a safe rule only to admini ever cases after confirmation of diagnosis of malaria by examination

PROGNOSIS

Yellow fever outbreaks whether of urban or jungle origin consist in great part of relatively mild cases many of which are never diagnosed Cases developing symptoms of intoxication on the other hand always merit a guarded prognosis The appearance of the patient is not a safe index to his real condition the rapidity with which a sudden failure of the myocardium may at any stage of the disease even during convalescence terminate an otherwise favorable case is hardly less dramatic than the swift change in prognosis determined by the unexpected onset of uncontrollable hemorrhage or by the complete suppression of the urine Apparently light cases in which the patient seems to be doing well can change overnight and show signs of severe intoxication in the second stage whereas cases with more than usual severity of onset with intense congestion and high temperature may enter into rapid convalescence after the first stage or may show a decided improvement between the first and second stages only to be overwhelmed by intoxication of the second stage

Oliguria is always a grave sign and the onset of anuria leaves little hope of recovery On the other hand uresis may be good especially in hemorrhagic cases right up to the hour of death Cases showing heavy albuminuria visible jaundice and copious hemorrhage are indeed poor risks and the development of hiccoughs coma or delirium often presages an early end When the pulse which has dropped after the first days of fever begins to rise especially in the presence of a falling body temperature it always must be looked upon with suspicion If a pulse of about 100 beats per minute is found after the third or fourth day in cases with jaundice and hemorrhage trouble must be anticipated The early appearance of intense jaundice is a bad omen Black vomit occurring in the first stage is due to partial digestion of blood from the nasopharynx or throat and is not indicative of serious intoxication as is the true black vomit of the second stage Melena is considered by clinicians as more serious than black vomit Albuminuria even when excessive is not in and of itself of prognostic importance

Recovery may come at any time and very unexpectedly Real miracles sometimes occur hemorrhages stop suddenly polyuria begins and convalescence is established by crisis Cessation of hemorrhage is one of the first signs of improvement disappearance of albuminuria the last Death from yellow fever may occur as early as the third and is most common between fourth and seventh days Patients living more than a week after onset have a good chance of recovery and deaths from uncomplicated yellow fever seldom occur after the tenth day

TREATMENT

Virus diseases are in general noteworthy for their variability in severity Yellow fever is an outstanding example of such variability but it is also a disease of uncertain prognosis Only with a knowledge of these characteristics

is it possible to understand the past acceptance and popularity of many forms of treatment for yellow fever since abandoned Once yellow fever has declared itself there are no known specific serologic or chemical therapeutic agents of value

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High temperature may be relieved by an ice-cap to the head and by tepid sponge baths Depressant antipyretic drugs should not be used In regions where yellow fever may be present it is a safe rule only to administer quinine to fever cases after confirmation of diagnosis of malaria by examination of blood film

PROPHYLAXIS

There are only two effective means of yellow fever prophylaxis available today namely antimosquito (antilarval) measures and vaccination Quarantine fumigation medical vigilance and isolation of active cases are because of various factors including the occurrence of many mild unrecognizable infections of only limited value The choice of method will depend on circumstances and whether the problem is being faced from the standpoint of the individual the community or the region

The protection test survey and viscerotomy have both been used for revealing the existence of the threat of yellow fever but of the two viscerotomy has been found most useful since it uncovers the presence of the virus through the discovery of fatal cases at the time they occur whereas the protection test survey only reveals the fact that certain individuals still living have at some time in their lives become immune to the disease Viscerotomy then should really be considered as an important part of the prophylaxis of yellow fever It gives warning of the necessity of vaccination for populations exposed to the jungle infection who are generally loath to present themselves for vaccination in the absence of a known local threat and furnishes essential information on which health officers throughout the continent may base their program for *A aegypti* elimination

Vaccination

Vaccination is the method of choice for individual protection and for the immunization of armies and mobile labor gangs and is the only protection available for populations exposed to jungle infection Vaccination should also be used for the crews and passengers of airlines operating between endemic and non endemic regions not only for their own protection but also to prevent them from being the vehicle for the virus from infected to non infected districts

In the Americas in England and in the British colonies in Africa vaccination has since 1937 depended on the use of a modified strain of yellow fever virus known as 17D which has lost in great part not only its viscerotropism but also in contrast with the strains previously used for vaccination much of its neurotropism

Virus 17D grows readily in chick embryo tissue and the infected embryo itself is used in the preparation of the vaccine The seven to nine day old embryo is inoculated through a small hole in the eggshell over the air sac After four days additional incubation the infected embryo is *harvested* pooled with others of the same lot and triturated The resulting paste is centrifuged and the sediment discarded The supernatant fluid is the vaccine material which for preservation and shipment is put in ampules in measured amounts and thoroughly desiccated in vacuum from the frozen state Residual moisture determinations should be made on sample ampules from each lot of vaccine prepared Vaccine containing less than 2 per cent residual moisture keeps well in sealed ampules in the ice box The vaccine is tested for potency by

inoculation of serial dilutions in mice and the amount of rehydrated material used for individual immunization with each lot of material prepared depends upon the results obtained

Only one inoculation is given Successful vaccination depends on delivering living virus under the skin of the persons being vaccinated As inactivated virus is not antigenic, every precaution should be taken to protect vaccine virus against moisture heat sunlight and other harmful agents *In the field* the ampules of desiccated virus should be kept in contact with ice in thermos containers and should be rehydrated only immediately before inoculation

Reactions to virus 17D are generally unnoted or consist only of slight head ache and malaise for some hours five to eight days after inoculation Delayed postvaccination jaundice and a mild encephalitis have been encountered in investigations of vaccinated populations but their etiology has not been clearly established

Field experience suggests that vaccination is effective almost immediately against infection through exposure although antibodies have not been dem onstrated until after the first week In many individuals the active immunity produced by virus 17D has persisted apparently unaltered during the four year period elapsed since the field use of this vaccine began Only after the lapse of a longer period can conclusions regarding its duration be drawn

Antimosquito Measures

From the standpoint of protecting the community against *aegypti* transmitted yellow fever antimosquito measures still hold first place in spite of the great success of vaccination in recent years A low mosquito density guar antees against yellow fever dengue and filariasis and makes for comfortable living while vaccination is difficult to carry to a large part of the local popula tion at a time when yellow fever is not known to be present

The dream of complete eradication of yellow fever from the Western Hemisphere through anti *aegypti* campaigns has not been realized only be cause of a permanent reservoir of virus in jungle animals the existence of which was unknown at the time that dream was formulated However the complete eradication of the *aegypti* borne yellow fever of history the only yellow fever which was recognized at the time the dream of eradication took shape is still possible not through the temporary reduction in *aegypti* density in the principal endemic centers as was anticipated but through the com plete eradication of this species itself which as far as is known is the only urban vector of importance To speak of species eradication some years ago was to invite doubts of one s sanity since a species was thought by many to be something sacred and eternal having an existence quite independent of the individuals composing it However work in Brazil first with *aegypti* and later with *Anopheles gambiae* has shown that a species is as vulnerable as its component individuals and that species eradication is feasible for some species when men money and authority are available to apply control measures

Anti *aegypti* campaigns should be devoted to the attack on the aquatic (larval and pupal) forms since only under very exceptional conditions will the highly expensive fumigation and spray disinsectization attack on the adult form show satisfactory results Fortunately *A aegypti* is at least in the Americas almost entirely an artificial water container breeder except for tree holes and rock pools It is never found in ground pools One of the principal difficulties in the eradication of *A aegypti* is the ability of the egg to withstand desiccation for many months on the wall of a water jar or other container and to hatch out rapidly when by chance it comes in contact with water once more

Both urban and rural anti *aegypti* campaigns are organized by assigning to each trained inspector a definite section or zone and making him responsible for seeking out and destroying on regular weekly visits to every house in his zone all actual and potential breeding foci A focus may be eliminated through destruction of the water container in which the focus is found or through the application of a mixture of fuel and diesel oils to the water within the water container Emptying the container is not a satisfactory method of destroying the focus since eggs and small larvae often remain to produce another focus immediately

Elimination of Residual Aegypti Breeding

Once this routine work of the inspector has reduced to a low figure the number of houses in which evidence of *aegypti* breeding can be found a special search can be begun for the presence of undiscovered breeding based on the finding of adult mosquitoes in houses where evidence of breeding is no longer being reported Such missed breeding has in the past often been responsible for the failure to eliminate the *aegypti* species from many towns which were worked and the discovery that it is possible to eradicate the *aegypti* mosquito from an area by searching out and destroying this residual breeding is a most important practical contribution to public health administrative practice The adult capture method has proved to be the most sensitive indicator of the presence of *aegypti* in an area and is invaluable in locating the position of such hidden primary perpetuating foci as may remain after the gross infestation has been eliminated by routine antilarval measures

Table V presents in summary form * annual reports of the actual number of premises † found with foci of *aegypti* in various cities of Brazil before and after the adoption of the program of species eradication based on adult captures and destruction of foci by routine oiling

* More details of this work from 193 to date have been published from time to time in the *Boletín de la Oficina Sanitaria Panamericana* Washington D C

† The house breeding index or percentage of houses found with *aegypti* foci is useful in estimating the possibility of yellow fever transmission and in comparing the situation of one uncontrolled city with another Once eradication is undertaken in an area the interest shifts to a comparison of local conditions at intervals in the same area over a period of time For this purpose the actual number of premises found with foci is a much more stimulating figure than is the house breeding index which often masks the trend of small numbers behind a series of decimal places

TABLE V

SUMMARY OF HOUSES FOUND WITH AEGYPTI FOCI BEFORE AND AFTER SPECIES ERADICATION PROGRAM

B I nu	A Po xi te	A N mb H xi te s	W k Be	B E S ci N		Art S cies E ad ati n House with Rei festat of aegypti			
				Yea	H ses th aegypti	938	939	94	94
Manáos	63 574	13 753	1933	1933	6 744	6	2	0	5
Belém	59 088	32 405	1929	1932	3 033	4	2	3	1
São Luiz	63 617	12 327	1928	1931	8 753	0	0	0	0
Ter z na	40 248	9 650	93	1932	7 832	0	0	0	0
Parnaíba	21 395	5 620	931	1933	1 245	0	0	0	0
Fort l za	1 2 2 3	28 206	1928	1931	1 086	11	2	2	0
Natal	50 630	12 501	1926	1931	20 720	0	0	0	0
Macau	7 469	966	1931	1931	519	1	0	0	2
João Pessôa (P aíb)	74 134	12 645	1926	193	106	0	0	0	0
C bedelo	6 322	1 704	1929	1932	427	0	0	0	0
Recife	333 600	76 684	1923	1931	20 085	0	0	0	0
Macei o	74 723	20 65	1929	1931	15 345	0	0	0	0
P nedo	12 559	3 970	1929	931	1 283	0	0	1	0
Arac ju	51 561	13 274	1928	1931	442	4	1	10	0
S lvador (B i)	255 166	58 252	1923	193	12 901	2	3	2	1
Ilheós	19 035	4 985	1930	193	9 598	0	0	0	0
Vito ia	61 635	13 586	1931	1931	5 996	0	0	0	0
N tero San Gonzalo	193 449	45 632	1930	1932	12 89	0	0	2	0
Fed ral D trict	1 87 440	383 713	1928	1932	899	1	0	0	1
Santos	43 351	27 612	1935	1935	190	0	0	0	0
Florianopolis	33 680	5 257	1936	1936	152	3	0	0	0
TOTAL	3 574 949	784 507	—	—	141 247	32	10	20	10

Mod fied from Soper Fred L and Wilson D Bruce Species erad cation a pract cal g al of species reduct on in the control of mosqu to borne disease *J N t Mal Soc* 1 5 1942

Species Eradication of Aedes aegypti

Whereas it has long been possible to eliminate yellow fever from a given community by reducing the breeding of *aegypti* mosquitoes only during the

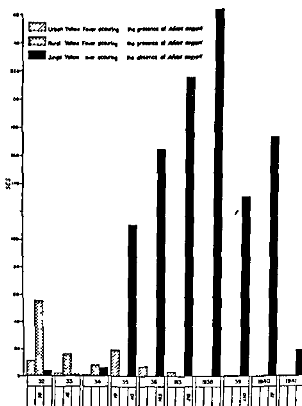


FIG 61 Incidence of urban rural and jungle yellow fever in areas infested by *Aedes aegypti* Brazil 1932–1941

past decade has it been possible to eradicate the species from a given community and to organize anti *aegypti* measures on such an economic basis that hopes can be entertained of permanency of control it has been shown that *after local species eradication of aegypti a very small sentinel staff making* occasional surveys is sufficient to protect a community against reinfestation from uncontrolled areas Naturally the larger the area from which the species has been eradicated the less the danger of reinfestation and the lower the per house cost can be made in the clean area This fact forces the consideration of *aegypti* eradication from the standpoint of states nations and even continents instead of that of individual cities

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CHAPTER XXXIII

DENGUE

CHARLES FRANKLIN CRAIG

DENGUE (BREAK-BONE FEVER SEVEN-DAY FEVER THREE-day fever giraffe fever ankle fever boquet fever) is an acute infectious specific disease caused by a filterable virus and transmitted from man to man by the mosquitoes *Aedes aegypti* and *Aedes albopictus* and probably by other mosquitoes as well It is characterized by a sudden onset severe pains in the muscles bones and joints typical skin eruption marked leukopenia severe prostration and a temperature curve showing a sudden initial rise a recession on the third or fourth day a secondary rise and a critical fall to normal or below on the fifth sixth or seventh day

HISTORICAL NOTE

Dengue fever was first described by Boylan in Java in 1779 and by Benjamin Rush in Philadelphia in 1780 In 1903 Graham produced the disease by the bites of mosquitoes which he stated were *Culex fatigans* but he must have had some *A aegypti* among those he employed in his experiment Bancroft in 1906 first definitely proved that the disease was transmitted by *A aegypti* Ashburn and Craig in 1907 proved that dengue was caused by a filterable virus and was not contagious In 1931 Simmons St John and Reynolds proved that *A albopictus* could also transmit the disease and that it could be transmitted mechanically by *Culex quinquefasciatus*

ETIOLOGY AND EPIDEMIOLOGY

Prior to the researches of Ashburn and Craig in 1907 dengue was regarded as a most contagious disease and the cause was believed to be of bacterial nature Several organisms had been described as the cause but not proved to be so In 1907 Ashburn and Craig working in Manila demonstrated by the inoculation of human volunteers with the filtered blood of dengue patients that the cause of dengue is a filterable virus present in the peripheral blood of the patient during the first four days of the disease They also proved that dengue is not contagious that some individuals are naturally immune and that an immunity follows an attack of the disease All of these observations

have since been confirmed by numerous observers especially *Siler* Hall and Hitchens Simmons St John and Reynolds and Chandler and Rice

The virus of dengue fever was proved by Ashburn and Craig to pass through a Lilliput filter that retained all known bacteria and other observers have shown that it will pass through several filters through which some other filterable viruses will not pass thus proving that it is of very small size and it has not been demonstrated with the microscope It was shown by Ashburn and Craig to be present in the blood during the third and fourth days of the disease and that in human volunteers the filtered and unfiltered blood of a patient during that period when inoculated subcutaneously or intravenously produced a typical attack of dengue after an incubation period varying be tween two and one half and seven days the average being four days According to Blanc Caminopetros and Manousakis (19 8) the virus is infective after being kept at o C (3° F) for two months and Findlay in London has successfully inoculated individuals with the blood of dengue patients which has been kept for long periods of time in a desiccated condition It can pass through the unbroken skin of man (Simmons St John and Reynolds 1931) and is filterable in the infected mosquito

Immunity follows an attack and probably is of comparatively short duration Sharp and Hollar (1935) maintain that it lasts for from one to four years but no virus neutralizing bodies have been demonstrated in the blood serum of immune individuals Animals cannot be protected from experimental yellow fever by the blood serum of patients recovered from dengue as shown by Snijders Postmus and Schuffner Only monkeys and guinea pigs have been found to be susceptible to dengue and in both of these animals the infection is not accompanied by clinical symptoms Simmons (1931) suggested that monkeys may act as reservoirs of infection for man and monkeys in regions where dengue is endemic have been found immune to the infection

The transmission of dengue from man to man is through the bites of certain species of mosquitoes especially *Aedes aegypti* Ashburn and Craig were successful in infecting a human volunteer with dengue by the bites of many *C fatigans* mosquitoes but this result was due to mechanical transmission as proved by Simmons St John and Reynolds (1931) How important such mechanical transmission is in epidemics of this disease is unknown

Other mosquitoes have been found capable of transmitting dengue Simmons St John and Reynolds found *A albopictus* in Manila to be as efficient a transmitter as *A aegypti* while Morishita (1925) in Formosa found that *Armigeres obturbans* and *Chandler and Rice in Texas (19 3)* found that *Aedes argenteus* transmit dengue to man In all probability other mosquitoes will be found to transmit the infection as in yellow fever

After biting an infected individual the mosquito does not usually become infective for from ten to twelve days but Schule (19 9) proved that it might become infective as early as eight days after the infective blood meal Simmons St John and Reynolds (1930) found *A albopictus* did not become infective until periods varying from thirteen to twenty two days had elapsed after biting

These differences are undoubtedly due to biologic conditions which vary from time to time

During the incubation period in the mosquito the virus multiplies until at the time the mosquito becomes infective it may be demonstrated in all parts of the body as well as in the salivary glands The infection in the mosquito persists during the life time of the insect and apparently has no evil effect so far as observations have shown

Dengue is a very rapidly spreading infection and in a non immune population affects a very large proportion of the people It is therefore a disease of great economic importance The conditions governing its rapid spread in a community are the presence of a large non immune population large numbers of mosquitoes suitable for its transmission and biologic conditions favoring its transmission

As dengue is usually transmitted to man by *A aegypti* and *A albopictus* it occurs in countries where these mosquitoes are present Dengue occurs in the Southern United States Panama Dutch Guiana Cuba Puerto Rico Ecuador Brazil Argentina in tropical Africa Australia the islands of the Pacific especially in the Philippines in Greece Palestine Syria Turkey Macedonia and the Dardanelles in India Ceylon Burma Indo China Cochin China Tonkin Dutch East Indies and Japan Extensive epidemics have been recorded in the United States in Alabama Georgia Florida Mississippi Louisiana and Texas within recent years

Dengue is not contagious as first proved by Ashburn and Craig (1907) and it is perfectly safe to treat dengue patients in hospital wards among other patients provided the wards are properly screened

PATHOLOGY

Dengue is a disease with an exceedingly low mortality—less than 1 per cent—and deaths usually occur only in the very young or in the old who are already suffering from debility caused by other conditions Thus practically nothing is known regarding the pathologic changes caused by the dengue virus in the body

Although the general pathology of this disease is not known the changes observed in the blood have been studied by numerous observers especially by Stitt (1907) Ashburn and Craig (1907) Vedder (190,) and Simmons St John and Reynolds (1931) Ashburn and Craig found that anemia did not occur in dengue that the erythrocyte count as well as the hemoglobin and color index remained normal Stitt and others have shown that a well marked leukopenia was present in dengue Ashburn and Craig found in their cases that the leukocyte count varied between 3 500 and 3 800 leukocytes per cmm but cases were observed in which the count was as low as 1 00 or as high as 5 000 leukocytes per cmm The leukopenia is progressive in character It is most marked on the fifth and sixth days of the disease but exceptions to this rule were noted Siler Hall and Hitchens (1926) state that 25 per cent of their cases of dengue failed to show leukopenia a most unusual finding

Besides the marked leukopenia the disease is characterized by a marked reduction in the number of polymorphonuclear leukocytes the latter being most numerous late in the disease In addition to the leukopenia and changes in the relative count of leukocytes Simmons St John and Reynolds (1931) showed that there is an enormous increase in the immature polymorphonuclear leukocytes that is a marked shift to the left in the Schilling count They regarded this together with the marked leukopenia as the most reliable single diagnostic sign of dengue In rare instances an increase in eosinophiles has been noted but this was probably caused by some complicating factor

SYMPTOMATOLOGY

Despite the usual textbook description of dengue which would indicate that the disease has a characteristic symptomatology there is perhaps no other disease in which the symptoms vary as greatly Cases occur that are so mild as to be clinically unrecognizable while others are so severe as to cause the prostration of the patient a few moments after the initial symptoms Many cases occur in which the symptoms are atypical

The *period of incubation* varies from twenty four hours to fifteen days In the many cases observed by Ashburn and Craig (1907) the period of incubation varied from three to eight days in naturally acquired infections and from two and one half to seven days after the inoculation of human volunteers with blood from dengue patients the average period being three and three-quarter days After experimental inoculation by infected mosquitoes Cleland Bradley and McDonald (1916) found that the incubation period was from six to ten days Siler Hall and Hitchens (1926) from four to six days and Simmons St John and Reynolds (1931) from three to eleven days the average being five and one quarter days Actually in nature both longer and shorter incubation periods have been observed

The *onset* of dengue is usually very sudden although a gradual onset is sometimes observed There are no prodromal symptoms in the vast majority of cases The patient apparently in perfect health is suddenly stricken with extreme weakness accompanied by headache aching in the muscles and a feeling of weariness in the arms and legs Chilly sensations may be present but a distinct chill is rare These symptoms rapidly increase in intensity the aching and pain in the muscles become almost agonizing in severe cases Pain is said to be felt even in the bones but this sensation is in the muscular attachments to the bones rather than in the bones themselves The headache is very severe and usually frontal in type the eye balls are sore to the touch and painful upon movement and in most cases there is marked postorbital pain Nausea and vomiting may be present The appetite is lost in fact anorexia is a common symptom The patient is usually depressed and in some cases somnolence and stupor may be present In children a mild form of delirium is common and convulsions have been observed In mild cases the symptoms of onset consist of slight headache and general malaise and may be so mild as to escape attention

During the onset of dengue the face is greatly congested the conjunctivae injected and the patient s expression is one of anxiety or excitement At this time the skin may show a definite erythematous flushing the so-called primary eruption of dengue but this is often absent or so evanescent as to be overlooked by the physician

The temperature in dengue rises rapidly and usually attains its maximum at the end of twenty four hours when it reaches 39 7 to 41 C (103 5 to 105 8 F) the average maximum being between 39 / to 40 C (103 5 to 104 F) In mild infections the temperature may not rise above 38 C (100 4 F)

In typical dengue the temperature curve is characteristic. The initial rise the period of intermission and the final rise followed by a critical fall are suggestive of dengue fever After reaching its maximum at the end of twenty four hours the fever begins to decline falling one or more degrees within a period of a few hours until it may even reach normal or usually a degree or two above normal where it remains with slight vacillations until about the fifth day of the disease It then rises again suddenly to a point as high or even higher than during the initial rise and then falls by crisis on the sixth day when the symptoms disappear completely This typical saddle back type of temperature curve (Fig 62) is often observed in severe cases of dengue and modifications of it are observed in milder infections It used to be considered diagnostic However many cases occur in which it is not present In some cases the temperature remains elevated for several days and then falls by crisis or there is only a day or two of fever with no period of intermission Still others occur in which the fever is so slight and the symptoms so negligible that the patient pays no attention to them and continues in his occupation These cases are most important from the standpoint of the transmission of the infection

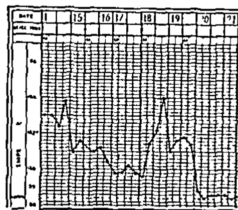
In those cases in which there is a distinct period of intermission in the temperature the symptoms become less severe but increase again in severity with the final rise in temperature

The *skin eruptions* which occur in dengue are most important from a diagnostic standpoint While the *primary eruption* probably occurs in all moderately severe cases of dengue it is often exceedingly transient lasting only an hour or a little longer and may be missed unless the skin is inspected frequently during the first twenty four hours or so of the disease It is not a true eruption but is due to a marked dilatation of the capillaries of the skin It appears on the face neck arms thighs chest and back on the arms and thighs it is situated on the inner aspect The condition resembles sunburn or the rash of scarlatina

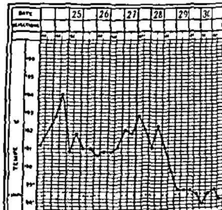
The so-called *secondary eruption* in dengue usually appears between the third and sixth days of the disease perhaps most frequently just before the final fall in the temperature although it may appear at the beginning of the secondary rise in the temperature or even during convalescence As in the case of the primary eruption it is often evanescent and may be easily overlooked

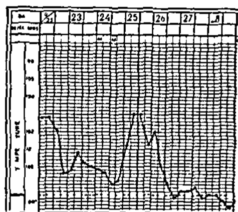
unless the patient is frequently examined It occurs most frequently on the trunk but may cover the entire body or it may be most marked on the wrists ankles thighs palms of the hands or on the neck It was present in our ex

A

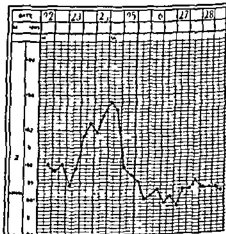


B





C



D

Fig 62 Typical temperature charts of dengue fever A B C Saddle back types showing variations in degree of remission D A common type without remission observed in mild infections (After Ashburn and Craig)

perience in over 75 per cent of the patients but it is probable that it occurs in practically all cases although it may be missed in the milder ones

From the descriptions of this eruption that have been given by different authorities it is evident that its character varies considerably in different individuals and in different epidemics macular maculopapular petechial measles like and scarlatinal forms of eruption have been described but in my experience the commonest form was an eruption resembling that of measles but with finer macules arranged in smaller groups and brighter red in color

Another type of eruption frequently observed resembles that of scarlet fever although less vivid in coloration In severe cases a petechial eruption *may appear as small purple or red dots superimposed upon the general eruption* most frequently on the buttocks and back Some authorities have described an urticarial eruption but we have never observed this type Itching often precedes or accompanies the eruption and may even persist during desquamation In moderately severe cases the eruption lasts about two days it may however disappear within an hour or so or may persist for a week or more The more *extensive the eruption the longer it persists When it is disappearing* a very fine desquamation may be noticed but it is not present in those cases in which the eruption has lasted only a short time In some persons a slight brownish discoloration of the skin appears after the disappearance of the eruption but I have never observed jaundice as have some other observers

The *pulse* during an attack of dengue increases in rate with the rise in *temperature but it is not as rapid as in other infections that are accompanied* by a similar degree of temperature I have not observed the marked slowing of the pulse described by some authorities and Faget s sign does not occur in this disease During convalescence the pulse is usually slow and of low tension

Hemorrhages are not common in dengue Epistaxis described by some authors as common at the onset of the disease was not observed by Ashburn and Craig or by Siler *Hall and Hitchens in any cases nor did Ashburn* and Craig observe hemorrhages from the stomach mucous membranes or intestines Most cases of so-called dengue in which such hemorrhages were seen were really cases of yellow fever Menstrual hemorrhages may occur and there may also be minute hemorrhages into the skin

Symptoms connected with the *alimentary tract* are common in dengue Anorexia nausea and vomiting *may occur at the onset and anorexia may per*sist throughout the attack Diarrhea may be present but constipation is more common Abdominal pain and colic are sometimes present and the abdominal muscles are usually tender upon pressure During the first day or two of the disease the *tongue* is somewhat characteristically coated with a cream colored fur which thickens and becomes darker toward the middle of the tongue while *disappearing from the edges By the third day it shows a clean tip and edges* with a heavy yellowish or brownish central coat Throughout the attack the tongue remains moist and fissures seldom occur

The *nervous system* is markedly affected by the dengue virus and most of the unpleasant symptoms are of nervous origin LeGac and Servant (1939) have found that the cerebrospinal fluid in dengue patients shows hypertension that there *is an increase in albumin* and sugar *but that the fluid is clear* and shows no increase in the cellular content They found that spinal puncture relieved all the headache and muscular pains as well as most of the other unpleasant symptoms of the infection

The various types of *pain* that usually accompany an attack of dengue have been mentioned in describing the onset of the disease In mild cases pain may not be a prominent symptom In most cases the severe headache *pain* and

aching in the muscles especially in the lumbar region and the arms and legs and the tenderness of the muscles are the most prominent symptoms of the disease The name break bone fever is not particularly appropriate since comparatively few patients complain of pain in the bones but sometimes the pain in the muscles is so severe and deep seated that the patient believes it is located in the bones

Insomnia may be a distressing symptom and is commonly observed while mild delirium may be present during the early days especially in children In the latter meningeal symptoms have been noted Mental depression is very common in dengue both during the course of the infection and in convalescence but this gradually disappears without any permanent disability

Symptoms connected with the *genito urinary system* are absent in dengue and unlike yellow fever there is no evidence of involvement of the kidneys Albuminuria and casts do not occur in the urine whereas these are invariably present in all symptomatic cases of yellow fever

Convalescence may be prolonged after an attack of this disease but it is usually rapid The patient frequently complains of a sense of mental depression and in rare cases this may be so severe as to prolong convalescence greatly

COMPLICATIONS AND SEQUELAE

Complications are rare in dengue and sequelae are almost unknown Bronchitis is sometimes observed as a complication and in very old patients pneumonia has been recorded as a cause of death

DIAGNOSIS

The *clinical diagnosis* of dengue rests upon the characteristic symptomatology of the infection when it is present However many cases occur that are so mild as to be unrecognizable clinically and others in which the symptoms are so atypical as to render the diagnosis impossible In the presence of an epidemic dengue is readily diagnosed but sporadic cases are often overlooked and serve as starters of an epidemic When present the characteristic saddle back temperature curve the eruption and the marked leukopenia accompanied by a relative increase in the mononuclear leukocytes and a shift to the left in the Schilling count are diagnostic of this infection

The *laboratory diagnosis* of dengue depends on the demonstration of marked leukopenia a shift to the left in the Schilling count and an increase in the mononuclear leukocytes Simmons and others believe that the leukopenia and the shift to the left in the Schilling count are practically diagnostic of the disease

The *differential diagnosis* of dengue from other acute infections is most important especially in regions where yellow fever occurs as the early recognition of the disease will prevent its extension and remove the fear that it may be yellow fever The diseases most frequently confused with dengue are yellow fever phlebotomus fever malaria scarlet fever influenza measles and syphilis but other diseases such as the relapsing fevers and certain forms of typhus fever may also be confused with dengue

Yellow fever and dengue frequently occur in the same regions and have frequently been confused The first cases of yellow fever in a community are usually called dengue and it is not until deaths begin to occur that the diagnosis is changed to yellow fever The two diseases are most likely to be confused in children as yellow fever in the child is usually a mild disease and greatly resembles dengue in its symptomatology It is impossible to differentiate these two infections in patients presenting very mild symptoms but in the average case of yellow fever the slow pulse with a high temperature (Faget s sign) the early appearance of albumin and casts in the urine jaundice hematemesis positive mouse protection test after the fifth day of the disease the absence of an eruption or of marked leukopenia accompanied by a shift to the left in the Schilling count should serve to distinguish yellow fever from dengue Unfortunately both diseases are often atypical in symptomatology and consequently it is very difficult to differentiate such infections

Malaria can be distinguished easily from dengue by the demonstration of the causative *Plasmodia* in the blood provided quinine has not been administered If quinine has been administered the fever will decline rapidly while in dengue it will be uninfluenced by the drug The absence of an eruption in malaria is of diagnostic importance as well as the more rapid pulse and the absence of a shift to the left in the Schilling count In malaria there is usually a marked reduction in the erythrocyte count while in dengue the erythrocyte count is practically normal

Phlebotomus fever is very apt to be confused with dengue The longer duration of the fever in the latter disease the saddle back temperature curve as well as the marked leukopenia and shift to the left in the Schilling count should serve to distinguish it from phlebotomus fever The milder cases of dengue fever in which the fever lasts only for two or three days are practically impossible to differentiate from phlebotomus fever

Scarlet fever in children especially may be confused with dengue because of the resemblance of the dengue eruption to the rash of scarlatina or scarlet fever Desquamation of the eruption may also confuse the picture but the desquamation in scarlet fever is of coarser type and much more marked than in dengue The presence of a sore throat in scarlet fever and the absence of the characteristic temperature curve and marked leukopenia of dengue should serve to distinguish scarlet fever

Measles may also be confused with dengue since the dengue eruption sometimes resembles that of measles However the presence of Koplik s spots the absence of a marked leukopenia and the presence of marked respiratory symptoms indicate the presence of measles

In the tropics *influenza* may be mistaken for dengue as respiratory symptoms may be absent or very mild and the severe pain and aching in the muscles with postorbital pain and headache may be as marked as in dengue The absence of an eruption the saddle-back temperature curve and the very marked leukopenia all point to influenza rather than to dengue In temperate regions epidemics of influenza usually occur in cold weather whereas dengue always ceases with the advent of frost.

Syphilis has on rare occasions been confused with dengue during the secondary eruptive stage The absence of lesions of the mucous membranes, the temperature curve the severity of the onset and the absence of a history of an initial lesion in dengue should serve to distinguish the two diseases

The differential diagnosis of dengue from other diseases depends on the clinical history symptomatology and the results of the various laboratory methods available as diagnostic aids

PROGNOSIS

The prognosis of dengue is excellent Deaths do not occur from this disease alone although it must be noted that deaths have been described as occurring in the very young or in very old and greatly debilitated individuals I have never observed a fatal case of this disease and it has been estimated that even when due to complications the death rate is much lower than 1 in 1 000 cases

TREATMENT

Mild cases of dengue require no treatment beyond rest in bed and the administration of acetylsalicylic acid in doses sufficient to control the muscular pains and headache In more severe cases symptoms are treated as they arise Rest in bed should be insisted upon but usually the patient is so prostrated that he goes to bed at once A cathartic preferably calomel followed by a saline should be administered at the beginning of the attack and the bowels should be kept open throughout the febrile stage and during convalescence The diet should be liquid or semi liquid and the patient should not be urged to eat if anorexia is present as it is in the most severe attacks If the temperature goes above 40 C (104° F) cold sponging should be employed if the patient does not object If the pain is very severe and is not controlled by acetylsalicylic acid a hypodermic of morphia should be administered Throughout the attack unlimited amounts of fluid by mouth may be allowed iced lemonade and fruit juices being especially agreeable to the patient During convalescence the patient should be confined to bed for the first two or three days and except in the mildest infections should not be allowed to return to his work for at least a week after his temperature has become normal

PROPHYLAXIS

The prevention of dengue consists in the destruction of the mosquitoes transmitting the infection the protection of people from their bites and the protection of the transmitting mosquitoes from infection from man Fortunately the mosquitoes transmitting dengue *A aegypti* and *A albopictus* are domestic varieties breeding in small collections of water either within or in close proximity to human habitations so that their destruction is comparatively easy These mosquitoes breed in flower vases tin cans broken bottles artificial and natural collections of water such as fountains fire buckets and cement troughs and cisterns These should be emptied and destroyed or screened to prevent the access of mosquitoes to them Larger collections of water may be

oiled or properly drained but this disease like yellow fever is essentially a disease transmitted by mosquitoes breeding in small domestic utensils most of which can be destroyed or properly guarded by frequent emptying If fire buckets for instance are emptied once a week the water being poured on the ground in a thin layer so that it will not form puddles any developing mosquitoes present will be destroyed

Patients suffering from dengue should be in a mosquito proof room or at least under a mosquito net for the first four days of the disease thus preventing infection of the transmitting mosquitoes Houses should be screened and a head net and gloves may be worn if desired during an epidemic The rubbing of various repellents on the skin such as oil of citronella or eucalyptus is useful in preventing mosquito bites and thus minimizing the chances of infection during an epidemic

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CHAPTER XXXIV

PHLEBOTOMUS FEVER

CHARLES FRANKLIN CRAIG

PHLEBOTOMUS FEVER (PAPPATACI FEVER SANDFLY FEVER three day fever summer fever Mediterranean dengue) is an acute specific fever caused by a filterable virus transmitted from man to man by the sandfly *Phlebotomus papatasii* It is characterized clinically by sudden onset a fever lasting three days and terminating by crisis muscular pains and gastrointestinal and nervous symptoms

HISTORICAL NOTE

This infection was first described by Pym in 1804 in the Mediterranean regions and later by English army surgeons who observed it in Malta where it was called Mediterranean dengue because the symptoms resembled those of dengue fever McCarrison who observed cases of the disease in India in 1903 was the first to suggest that it might be transmitted by sandflies In 1907 following the work of Ashburn and Craig on dengue fever Doerr Franz and Taussig demonstrated that it was caused by a filterable virus transmitted from man to man by the sandfly *P papatasii*

ETIOLOGY AND EPIDEMIOLOGY

Doerr Franz and Taussig (1907) proved that phlebotomus fever was caused by a filterable virus by allowing infected sandflies to bite human volunteers in Vienna where the disease had not previously occurred They showed that infection followed such bites and that there was virus present in the blood only in sufficient amounts to infect the sandflies during the first twenty four hours following onset of the fever These findings were proved by injecting *volunteers intravenously with blood from patients suffering from* the disease In 1908 Birt confirmed the work of Doerr Franz and Taussig by producing phlebotomus fever in human volunteers in Netley England where it had never previously been found by means of the bites of infected sandflies

The virus according to Doerr Franz and Taussig passes through Berkefeld Reichelt and Pasteur Chamberland (Candle F) filters but it is retained by the Puckall filter through which the dengue fever virus passes Doerr held

that the virus was hereditary in the sandfly but this view has not been confirmed The exact period of infectivity of the fly has not been ascertained The virus may be kept for several days in infected blood at low temperatures Pandit Rao and Shortt (1938) cultivated the virus upon the chorio allantoic membrane of chicks and were able to maintain it in culture for long periods of time By means of cultures they ascertained that the virus was present in the blood of infected individuals for seven days These authorities have used with some success in the prevention of infection a vaccine prepared from the cultured virus The intravenous injection of infected blood into monkeys is followed by a febrile attack of short duration

Phlebotomus fever is an epidemic disease that occurs usually in subtropical and tropical regions but it is usually restricted to low lying moist localities especially to the coastal regions of the countries in which epidemics have been studied Owing to the resemblance in symptomatology to dengue and the extreme difficulty of differentiating these diseases when they appear together the exact *geographical distribution* of phlebotomus fever is probably unknown It has been observed in Mediterranean countries in Corsica Sicily Malta Cyprus Crete France the Balkans Egypt Turkey Syria Palestine Mesopotamia as well as in the Sudan Uganda India Federated Malay States Indo-China and China In the Western Hemisphere the disease has been observed in Argentina Brazil Guatemala Ecuador Central America and the coastal regions of Mexico It probably occurs wherever the transmitting sandfly *P papatasii* is found Although epidemics are usually found in low lying regions they have been observed in the Caucasus and in the Himalayas at altitudes of 4 000 feet

In temperate regions the disease appears in the summer months when sand flies are most numerous It usually comes in epidemics but it may be endemic, and therefore non immune individuals may become infected at any time if infected flies are present In temperate regions adult sandflies do not live through the winter The persistence of the disease can be explained only on the hypothesis that there is hereditary transmission through the eggs and larvae of infected flies or that there are human carriers Neither of these assumptions has been proved although Moshkovsky and his co-workers in Moscow state that the virus may be transmitted to the eggs and larvae of infected sandflies as was first maintained by Doerr and also that the feeding of the larvae on the feces of the infected adult flies is not necessary to convey infection to them as formerly believed In the endemic regions natives are usually immune and although second and even third attacks have been described a more or less lasting immunity is conferred by an attack Shortt Poole and Stephens (1936) showed that the virus is present in the blood in an infective condition for forty-eight hours in some cases although Doerr and his colleagues state that it is present for only twenty four hours after the onset of the disease Whittingham believes that the virus may persist through the winter in the soil of endemic regions but this has not been demonstrated

So far only one species of sandfly *P papatasii* has been proved to transmit

this disease but it is probable that other species may also be concerned *P papatasii* lays about forty eggs selecting crevices in damp walls cellars, caves latrines and other shaded moist places Its life cycle from the laying of the eggs to the imago is completed in about one month in subtropical and tropical regions but takes as long as two months in temperate climates After biting an infected individual the fly does not become infective until a period of six or seven days has elapsed So far as is known it then retains its infectivity as long as it lives Sandflies bite both by day and night As they fly for very short distances only phlebotomus fever is usually a house infection The disease is not contagious as was believed for many years Since the flies do not fly high individuals living above the first stories of buildings are usually in less danger of being infected than those living on the first stories Temperatures below 1 C. (70 F) are usually fatal to sandflies thus explaining the prevalence of the disease in the subtropics and tropics Epidemics of phlebotomus fever vary in severity according to whether conditions are unfavorable or favorable for the breeding of these insects

While phlebotomus fever and dengue fever closely resemble one another clinically an attack of one does not protect the patient against an attack of the other The immunity following phlebotomus fever is much more lasting than that following dengue fever

PATHOLOGY

As death from uncomplicated phlebotomus fever is practically unknown there is no knowledge of the pathology of the lesions which may accompany an attack of this disease All deaths recorded of patients suffering from the disease have been caused by complications and the autopsy findings have been those of the complications causing death The most important change observed is in the *blood count* since this disease like dengue is accompanied by leukopenia The leukocyte count usually varies between 2 500 and 4 000 per cmm with an increase in the mononuclear and a decrease in the polymorphonuclear leukocytes The *urine* is reduced in amount the specific gravity is increased and rarely a slight trace of albumin may be present The diazo reaction is negative and the virus is not present in the urine

SYMPTOMATOLOGY

The *incubation period* in naturally acquired infections varies between four and seven days The *onset* is usually sudden although prodromal symptoms consisting of malaise headache and slight muscular pains may sometimes be present Usually the patient suddenly complains of severe headache aching in the back loins and muscles The temperature is found to be elevated The symptoms increase in severity and the temperature rises until it reaches a maximum (Fig 63) of from 38 9 to 39 4 C (101 9 to 103 F) or higher but temperatures higher than 40 C (104 F) are very rarely observed The maximum temperature is reached in from twenty four to thirty six hours The fever continues for a day or two and then falls by crisis the entire febrile

attack, usually covering three days, although mild cases in which fever lasts only twenty-four hours and very severe cases in which it may last four or more days have been observed. In cases in which the febrile attack has been said to

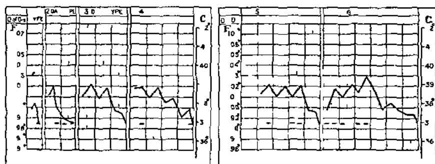


Fig 63 Typical temperature charts of phlebotomus fever (After Birt)

last for seven or eight days it is probable that the patients were really suffering from dengue fever. Afebrile infections have been reported and it is undoubtedly true that mild infections occur that are not recognizable clinically and that these probably have much to do with the spread of the infection.

After the fever has reached its maximum the patient suffers from severe supra-orbital headache, pain behind the eyes, intense aching in the muscles of the back and extremities, severe muscular pain especially marked in the lumbar region and rarely over the epigastrium. Constipation is usually present, but diarrhea may occur. Vomiting may be noted early in the disease. Anorexia is present and may be pronounced. The patient is usually drowsy, but insomnia may be present. In very severe cases there may be slight delirium, and convulsions have been observed in children.

During the height of the fever the face appears very much flushed, the conjunctivae congested, and there is marked tenderness of the eyeballs upon pressure. The tonsils and mucous membranes of the mouth and pharynx are congested, the tongue is covered with a yellowish white fur, the sides and tip being red and clean. There may be a slight nasal catarrh and in rare instances a mild type of bronchitis may develop. As in dengue the sense of taste is markedly affected and sometimes is lost altogether.

The skin in phlebotomus fever is hot, dry and greatly flushed. Sometimes an erythematous eruption appears to be present, while a subcuticular mottling of the skin is frequently observed. Cases have been described in which a papular eruption appeared toward the end of the febrile period, but here again dengue may have been confused with phlebotomus fever. Sweating sometimes occurs during the decline in the fever. Symptoms of collapse have been noted infrequently at this time. In rare instances hemorrhage from the bowels and epistaxis have also been noted. The glands are not enlarged and the liver and

this disease but it is probable that other species may also be concerned *P papatasii* lays about forty eggs selecting crevices in damp walls cellars caves latrines and other shaded moist places Its life cycle from the laying of the eggs to the imago is completed in about one month in subtropical and tropical regions but takes as long as two months in temperate climates After biting an infected individual the fly does not become infective until a period of six or seven days has elapsed So far as is known it then retains its infectivity as long as it lives Sandflies bite both by day and night As they fly for very short distances only phlebotomus fever is usually a house infection The disease is not contagious as was believed for many years Since the flies do not fly high individuals living above the first stories of buildings are usually in less danger of being infected than those living on the first stories Temperatures below 21 C (70 F) are usually fatal to sandflies thus explaining the prevalence of the disease in the subtropics and tropics Epidemics of phlebotomus fever vary in severity according to whether conditions are unfavorable or favorable for the breeding of these insects

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Yellow fever may be confused with phlebotomus fever if the infection is very mild but in the usual yellow fever infection the characteristic temperature curve the presence of albumin in increasing amounts in the urine and the development of jaundice easily distinguish the two infections *Influenza* may be distinguished by the presence of the respiratory symptoms but in the tropics influenza may occur without marked respiratory symptoms and in such cases a differential diagnosis is difficult and sometimes impossible *Para typhoid* infections may be distinguished by the longer duration of the fever *and the relapsing fevers by the occurrence of one or more relapses after a definite* afebrile period and by the presence of spirochetes in the blood

Laboratory diagnosis of phlebotomus fever is not possible With the exception of the examination of the blood for leukopenia there is no specific laboratory procedure of diagnostic value But even the presence of leukopenia is by no means specific for this infection because it is also a symptom in dengue and influenza In the differential diagnosis of the infections confused with this disease laboratory procedures are most important and should be largely relied on because they afford a means of differentiating between most of these diseases and phlebotomus fever

PROGNOSIS

The prognosis of this infection is always excellent as death never occurs in uncomplicated cases Complications are very rarely observed and are very seldom fatal

TREATMENT

No drug has been found of specific value in the treatment of phlebotomus fever At the present time treatment is on a purely symptomatic basis At the beginning of the attack the bowels should be opened with a saline cathartic the patient made to keep to his bed and the symptoms treated as they arise Pain is best relieved by acetylsalicylic acid (aspirin) in doses of 0 325 gm (5 grains) every three or four hours Rubbing the painful muscles with a liniment is often helpful Constipation should be appropriately treated and diarrhea if present may be alleviated by subcarbonate of bismuth The disease is of short duration and little treatment is required beyond keeping the patients as comfortable as possible Food should not be urged as there is usually more or less *anorexia present and it is better to keep the stomach unirritated Iced* drinks such as lemonade are often enjoyed when food cannot be taken If food is given it should consist of a semifluid diet and a full diet should not be resumed until convalescence takes place During convalescence the administration *of tonics and a full diet will hasten complete recovery*

PROPHYLAXIS

As the virus of phlebotomus fever is present in the blood during the first forty eight hours after the appearance of symptoms the patient should be in a mosquito-proof room or beneath a bed net in order to prevent infection of the transmitting flies Sandflies are so small that they easily pass through ordinary

spleen are normal in size The pulse is slow in comparison with the height of the temperature This may be a prominent symptom even late in convalescence The lungs heart and kidneys are normal An eruption of vesicles is present upon the mucous membranes of the palate and pharynx in some patients. LeGac Samara and Servant (1939) found that the cerebrospinal fluid is under increased pressure and that the amount of albumin is increased but that cells are few in number Tenderness of the articulations is present but no swelling takes place The changes in the blood have already been noted (page 434)

Convalescence from even moderately severe attacks is slow It begins immediately after the critical fall in the temperature and is usually accompanied by a considerable degree of mental depression The amount of debility produced by this infection is remarkable, considering the character and duration of the symptoms Relapses may occur but are rarely observed and convalescence is completed in from three to four weeks

COMPLICATIONS AND SEQUELAE

The most common complications include intestinal hemorrhage parotitis orchitis nephritis and bronchopneumonia but they are seldom observed There are no sequelae of consequence save the debility mentioned which may persist for some weeks

DIAGNOSIS

As *clinical diagnosis* of phlebotomus fever is extremely difficult in many instances especially in the very mild infections many such infections go unrecognized In the early stage of the disease a clinical diagnosis is impossible *because the symptoms are the same as those in any acute febrile* condition But the occurrence of a fever lasting for three or four days having sudden onset and accompanied by leukopenia intense muscular pains and bradycardia is most suggestive of phlebotomus fever provided such symptoms occur in individuals living in a region where sandflies (*P papatasii*) are present or in individuals who are known to have been in such regions

The *differential diagnosis* of phlebotomus fever is often rather difficult The diseases with which it is most often confused are dengue malaria yellow fever typhus influenza paratyphoid infections and relapsing fevers of short duration

Dengue fever is the disease with which this infection is most likely to be confused and in mild infections it is impossible to differentiate the two diseases with certainty In phlebotomus fever the shorter duration of the fever the lack of a secondary rise in temperature after a pseudocrisis the absence of glandular enlargement and of the terminal eruption should serve to differentiate it from dengue *Malaria* may be confused with this disease but the examination of the blood for the *Plasmodia* should settle the question while the absence of leukopenia in malaria is also a helpful diagnostic guide *Typhus fever* during the first three or four days may be mistaken for phlebotomus fever but the typhus eruption and the much greater prostration in typhus should distinguish them

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SMITH R O A MURKERJEE S HALDER K C and LAL C Bionomics of P argentipes duration of life in nature *Indian J M Research* 24 293 1936
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mosquito netting. Consequently a netting containing at least twenty-two holes to the linear inch is required even if, as in the tropics, such netting is very disagreeable because it excludes much air. As these insects do not fly much higher than 10 feet, the removal of patients to the second story of houses is a good prophylactic measure. To avoid infection one should sleep at least 12 feet above the ground if possible. The employment of electric fans in rooms is effective in prophylaxis since the flies will not enter rooms in which there is a strong current of air. The clothing should cover as much of the body surface as possible. The wrists and ankles should be smeared with a repellent, such as oil of citronella, anise, clove, or eucalyptus mixed with liquid petrolatum or lanolin. Camphor is obnoxious to the flies and, according to those who have used it, a piece carried in the clothing or placed in the bed acts as an efficient repellent.

The prevention of the breeding of sandflies is theoretically the most useful method of prophylaxis but this is often very difficult. These flies breed wherever there is darkness and moisture. It is difficult to remove many of the breeding places such as cracks in the ground or in buildings, but much may be accomplished by burning all rubbish about dwellings, by filling in cracks wherever possible with suitable materials, and by seeing that buildings are not surrounded by shrubbery or vines which may harbor the flies. All broken-down walls or buildings should be destroyed, latrines fumigated with sulphur, and dark cellars well ventilated and white washed. Premises in which cases of the disease have occurred should be avoided because the sandflies in such localities are almost invariably infected, and while it has not been absolutely proved that the virus passes from the infected insect into the eggs and larvae and is thus perpetuated, there is sufficient evidence to warrant the avoidance of all localities in which the disease has appeared.

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material within the nucleoplasma The nature and composition of these intranuclear inclusions are not known (Findlay) From the blood liver and spleen Daubney and Hudson isolated a filterable virus which according to Broom and Findlay measures from 3 to 35 millimicrons and is well beyond the limits of visibility by ordinary staining techniques microscopy or ultra violet photography It is resistant to glycerine and to the usual methods of preservation it grows well in tissue cultures of the Li Rivers type and preserves its characteristics through many passages The virus is highly pathogenic and invariably lethal to a variety of rodents (mice rats hamsters guinea pigs and rabbits) mongooses frogs and birds are resistant About 50 per cent of the rats and ferrets may succumb to infection The experimental animal of choice is the mouse

Epidemiologically of interest is the fact that cows goats squirrels and monkeys suffer from a non fatal malady following the injection of the virus Through intracerebral passage the pantropic virus may acquire neurotropic properties When administered intranasally it may produce pneumonias The virus has many features in common with that of yellow fever Both viruses exhibit acidophilic intranuclear inclusions in the liver and confer a lasting immunity to man following one attack but experimental studies have failed to reveal the existence of any cross immunity between these agents

Under natural conditions the transmission of the virus follows the principles of a heterogeneous infection chain Daubney Hudson and Garnham suspect the mosquito *Taeniorhynchus brevipalpis* while others incriminate *Mansonia* varieties Direct contact transmission from the infected animal to man through an abrasion of the skin through the conjunctiva perhaps through inhalation (Francis and Magill) is apparently the customary pathway in laboratory infections

Based on neutralization tests on serums Rift Valley fever is apparently prevalent in the Kenya Colony Uganda of British East Africa Anglo Egyptian Sudan French Sudan and French Equatorial Africa it has not been reported from Nigeria the Gold Coast Sierra Leone or Gambia (Findlay Stefanopoulo and MacCallum)

PATHOLOGY

With the exception of one fatal infection in a laboratory worker who died on the forty fifth day after the onset from thrombosis in the inferior vena cava and to a lesser extent in the saphenous and femoral vein no autopsy records are available Chronic pleurisy together with pulmonary infarcts and emboli was present Intestinal or hepatic lesions characteristic of the disease in sheep were not noted doubtless due to the fact that the active stage had subsided several weeks prior to death

SYMPTOMATOLOGY

Rift Valley fever in man has been described as dengue like or influenza like It is characterized by sudden onset fever and severe pains in the back and

CHAPTER XXXV

RIFT VALLEY FEVER

K. F. MEYER

RIFT VALLEY FEVER AS A DISEASE OF MAN HAS BEEN OBSERVED concurrently or secondarily during the course of a zoonosis—enzootic hepatitis—among sheep and cattle in *Central Africa*. *It is* caused by a virus and is probably propagated by mosquitoes, although ticks are likewise suspected as vectors. The incubation time is from five to six days, and the onset of the attack is characterized by a period of general malaise followed by rigors and headache. A saddle back temperature, severe bodily pains and leukopenia gives the disease a dengue like or influenza like character. However, the illness lasts only a few days and convalescence is short and uneventful.

HISTORICAL NOTE

On a farm in Kenya in 1912 Montgomery first saw Rift Valley fever as a septicemic infection of lambs, now designated enzootic hepatitis, with a case mortality of 90 per cent. However, it was not until 1931 that Daubney, Hudson and Garnham through systematic studies established epidemiologic deductions and the infectivity for man of the blood of the diseased sheep as a result of direct inoculation experiments. Almost every native engaged in herding sheep, approximately 200 human beings, became ill for a short period; they all recovered without complications or death. In the course of the study of the virus in Kenya, in England and in the United States at least sixteen professional *infections attest to the very high infectiousness of the* Rift Valley agent (Kitchen, and Francis and Magill). Similarity and dissimilarity between yellow fever and enzootic hepatitis were carefully analyzed by Findlay and his associates (1936).

ETIOLOGY AND EPIDEMIOLOGY

The natural disease of sheep is of a variable but in general of an exceedingly rapidly fatal character. Vomiting, diarrhea, purulent nasal discharge, abortion in pregnant animals, together with a normal temperature have been reported. At autopsy the liver reveals the lesions of acute yellow atrophy with extensive necroses. Histologically the *liver cells present varying degrees of disintegra*tion. Those with hyaline degeneration have the appearance of acidophilic

material within the nucleoplasma The nature and composition of these intranuclear inclusions are not known (Findlay) From the blood liver and spleen Daubney and Hudson isolated a filterable virus which according to Broom and Findlay measures from 23 to 35 millimicrons and is well beyond the limits of visibility by ordinary staining techniques microscopy or ultra violet photography It is resistant to glycerine and to the usual methods of preservation it grows well in tissue cultures of the Li Rivers type and preserves its characteristics through many passages The virus is highly pathogenic and invariably lethal to a variety of rodents (mice rats hamsters guinea pigs and rabbits) mongooses frogs and birds are resistant About 50 per cent of the rats and ferrets may succumb to infection The experimental animal of choice is the mouse

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SYMPTOMATOLOGY

Rift Valley fever in man has been described as dengue like or influenza like It is characterized by sudden onset fever and severe pains in the back and

extremities. After an incubation time of from five to six days and a very brief period of general malaise, nausea, vomiting and occasional diarrhea, sharp rigors and headache usher in the symptoms of the disease. The pyrexia may vary from 38.5° to 39.5° C (101.3° to 103.1° F) but it may occasionally reach 40° to 41° C (104° to 105.8° F) with a correspondingly increased pulse rate. During the first two days it gradually decreases until it reaches normal on the third or fourth days. Recovery may then take place in an uninterrupted manner; otherwise a second rise of temperature may occur. The second rise in temperature is seldom as high as the first, but when present shows graphically on the chart the well known "saddle back" type of pyrexia that was first noted in dengue. After the rigors have passed, pains develop in or near joints. These pains extend from the base of the skull to the extremities, sometimes localizing in the shoulder region. The face is brightly flushed and the patient complains of tenderness of the eyeballs and photophobia. Sleeplessness, anxiety, mental confusion, vertigo and some epistaxis are not uncommon. There may be a slight cough, a red throat, and a sense of fullness over the liver. During the second temperature reaction, three to four days after recovery from the initial attack, similar symptoms appear.

The convalescent period is short, although relapses on the tenth day after the onset have been observed (Francis and Magill). Usually convalescence proceeds without noteworthy complications except some pain on motion of the eyes and a sense of unbalance. Leukopenia, a very important and characteristic alteration in the blood picture, accompanies these symptoms. The decline principally affects the polymorphonuclear leukocytes; the white blood cells may drop below 3,000 per cmm. and the disease may persist into the convalescent period. According to Findlay, occasional myelocytes and polyblasts possess vacuolated nuclei. Although the urine of the patient appears to be normal and contains neither blood, bile nor casts, occasionally a deep yellow colored excretion may be encountered.

DIAGNOSIS

On purely clinical grounds a differentiation between Rift Valley fever and influenza or dengue is difficult under ordinary circumstances. There are no distinctive clinical features which could serve to differentiate one infection from the other. There are no reports in the literature on this subject which would indicate hepatic damage of sufficient intensity to render it clinically recognizable. If this should occur, the differentiation of Rift Valley fever from a mild attack of yellow fever would be equally a diagnostic problem of considerable magnitude. With the aid of laboratory tests the close similarity of the clinical course in Rift Valley fever and in influenza or dengue may be etiologically clarified. Blood of the patient withdrawn during the febrile attack and inoculated into mice subcutaneously or intraperitoneally induces within three to four days a rapidly fatal infection with characteristic liver necroses if the infection is caused by the Rift Valley fever virus. Even after intranasal infection, involvement of the respiratory tract with pulmonary lesions, essential

for the influenza virus is never observed Mice are not susceptible to the dengue virus In case the patient s blood is non infectious to mice nasal or throat washings may be tested in laboratory animals or the individual s serum should be tested for the existence of virus neutralizing or complement fixing *antibodies* The *latter* appear about fourteen days after the date of infection while the *former* have been shown to persist in human serum from four to five years after an attack Obviously these tests diagnose a Rift Valley fever in fection in retrospect provided the facilities for such a type of laboratory ex amination are accessible to the clinician in the tropics

PROGNOSIS

Rift Valley fever is a mild febrile disease with good prognosis However virus diseases are in general noteworthy for their variability in severity Thus in rare instances an infection may be followed by thrombophlebitis which may terminate fatally (Schwentker and Rivers)

TREATMENT

There is no specific treatment for Rift Valley fever The management of the cases reported has been symptomatic Absolute rest in bed and abstinence from food with the exception of fruit juices or alkalized water are indicated A high temperature may be relieved by an ice cap on the head or by tepid sponge bath Depressant antipyretics should not be used Activity during convalescence should be resumed gradually

PROPHYLAXIS

The suppressive measures employed in the Kenya Colony have reduced the exposure of pregnant ewes and newborn lambs (1) by removing the flock to higher country (7 000 to 8 ,00 feet elevation) into a mosquito free area or ( ) by planning the lambing season to fall at a time (October November) when the vector is not normally active So far nothing definite is known con cerning protective vaccination in the field although experiments in control measures have been reported by Stefanopoulo and Nagano Theoretically reduction of the disease in the animal reservoir should correspondingly diminish the number of infected mosquitoes and with it the risk of human infections

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CHAPTER XXXVI

PSITTACOSIS OR ORNITHOSIS

K. F. MEYER

PSITTACOSIS OR ORNITHOSIS IS ONE OF THE RARER OR LESS known forms of respiratory infection caused by a filterable microbial agent *Microbacterium multiforme psittacosis* (ornithosis). Household epidemics are recognized by the physician when he discovers in the home recently acquired parrots or parakeets, rarely finches or canaries, as cage pets which may or may not be visibly sick. Single patients with atypical pneumonias with unknown exposure to birds are, as a rule, correctly diagnosed with the aid of serologic tests or by isolation of the virus from the sputum. The word "psittacosis" from "psittacus" (parrot) suggested by Morange (1895) is primarily used to designate the contagious disease which follows contact with psittacine birds, while "ornithosis," as proposed by Meyer, is reserved for the same type of illness when the source is epidemiologically traced to petrels, pigeons, or chickens.

It is difficult to be certain of the exact time of infection because contact with the infected birds may spread over a considerable time. From epidemiologic studies it appears to be usually from seven to fifteen days. Since incubationary latency cannot be excluded, it is not surprising to observe occasionally an incubation time of from thirty to forty days. The disease is characterized by a fairly acute, although sometimes vague, onset consisting of feverishness and malaise without definite physical signs. However, toward the end of the first week the whole aspect of the disease becomes more severe and signs develop in the form of patchy migrating areas of consolidation, involving at first one segment of one lobe and then the major part of one or both lobes with little involvement of the bronchi and sputum. Obstinate constipation, abdominal discomfort, profound exhaustion, somnolence, and toxemia entirely out of proportion to the clinical findings predominate. At the end of from two to three weeks the temperature begins to fall by lysis and the patient gradually improves, but convalescence is protracted, tedious, and may be interrupted by relapses. In addition mild, ambulatory, rudimentary, and inapparent cases occur, though to be sure individual reactions to psittacosis infection may show completely different degrees of severity.

HISTORICAL NOTE

In the scientific report by Ritter in 1880 on a pneumotyphus epidemic among some relatives who had recently received a consignment of sick birds from Germany a disease of parrots was associated with a new distinct clinical entity manifesting itself as an atypical pneumonia The malady became generally known *through the localized outbreaks of severe pneumonia* which occurred in Paris in 1892 and in Germany in 1899 and 1909 From a rare disease psittacosis was suddenly raised to a malady of world wide interest when in 1929–1930 it appeared in Europe and the United States as a sequela to shipments of sick parrots from South America particularly Argentina and Brazil This pandemic with approximately 750 to 800 human cases the subsequent endemic distribution of parakeet psittacosis—recognized by K F Meyer and B Eddie Fortner and Pfaffenberg as well as by Haagen and Kruckeberg—involving in the United States and Germany another 600 victims and the examination of thousands of psittacine birds offered a splendid opportunity to many investigators for a thorough study of the disease from a clinic, etiologic and epidemiologic point of view

ETIOLOGY

Almost simultaneously in the early months of 1930 Levinthal in Germany Lillie in America and the British microscopist Coles discovered the presence of minute intracellular bodies within affected reticulo endothelial cells of diseased birds mammals and human beings These bodies are readily demonstrable with Macchiavello Castaneda or Giemsa stains in infective material The *Microbacterium multiforme* is cultivable in tissue cultures it contains two antigens one resistant to boiling and the other destroyed at this temperature (Bedson) Not very resistant to glycerine it is well preserved by desiccation and at a temperature of minus 76° C It is quite heat labile (15 minutes at 70° C) but remains infectious for ten days when treated in dense suspensions with 0.5 per cent formaldehyde and held at room temperature

Experimentally the virus has been transmitted to a great variety of psittacine birds to ricebirds sparrows finches canaries and pigeons and to white mice guinea pigs and monkeys

EPIDEMIOLOGY

Evidence although fragmentary strongly incriminates psittacosis as an almost universal low grade infection of parrots It is not confined to the Australian region which has as many species of parrots as the other five zoogeographical regions combined but extends to South America as many recent importations of these birds have amply proved This enzootic psittacosis among parrots in the wild has been fully established through the observations of Burnet and Meyer and Eddie As a rule it takes the form of a latent inapparent infection producing no visible symptoms or any pathologic signs beyond an enlarged spleen The birds doubtless become infected in the nests and remain immune to *reinfection* from other sources Variations from this condition may

tavor either host or parasites High mortality rates in zoological gardens are due either to the fact that the parrots escaped nest infections and so fell vic tim to infection from other sources or that the disturbances in the environment (low temperature crowding in insanitary cages improper feed) induced re lapses Infection spreads rapidly from bird to bird Under the circumstances it is not surprising if birds that are apparently healthy when captured in the bush or in the jungle are found to be suffering from psittacosis by the time they reach their ultimate purchasers and are capable of infecting their owners or other birds that come in contact with them in a pet shop or dealers storage pens Thus finches and canaries become diseased merely through con tact with infected psittacine birds The belief that psittacosis is solely a dis ease of the parrot family must now be considered ill founded in view of the facts that Haagen and Mauer in 1939 showed that in the Faroe Islands the fulmar or petrel (*Fulmarus glacialis*) is infected and that in both these is lands and in Iceland since 1930 174 human infections have occurred originally described as primary epidemic alveolar pneumonia (Rasmussen)

Even more disconcerting is the cumulative evidence which incriminates vari ous domestic pigeons (*Columba livia* var *domestica*) as the bird sources asso ciated with human cases of ornithosis

Human case to case infections are by no means infrequent (Meyer) Profes sional nurses or persons who care for psittacosis patients are often infected even ward infections have been reported (Pinero Garcia 1940) In fact chain transmissions have been observed in which a patient infected his nurse who in turn transmitted the disease to a woman patient of the hospital ward

The pathways of transmission from bird to man are twofold (*a*) by the aerogenic route—inhalation of droplet nuclei or dust contaminated with infective particles derived from desiccated fecal droppings urine feathers cadavers and the like and droplets from nasal secretions coughing of pa tients and (*b*) rarely by direct traumatic contact through a bite wound Contrary to general belief among the laity actual contact or possession of diseased psittacine birds is not necessary to transmit the infection since air currents may disseminate the virus particles

In certain occupational groups particularly those associated with the bird fancying trade there is a definitely greater incidence of the disease than in the average population However conclusive evidence shows that the apparent immunity of these groups is due to inapparent subclinical infection or inherent resistance (Meyer) The majority of psittacosis infections have occurred in people of middle age (66 per cent over the age of forty (Sturdee and Scott) the disposition to clinical psittacosis is very low in children under ten years of age The greater frequency of psittacosis in women (in California the ratio of women to men is 2 1 in Germany 17 8) is in part due to the fact that women are either engaged in the breeding of parakeets or that as lovers of pets they come more frequently in contact with the birds In the population at large the sexes are fairly equally represented The case fatality rate of the reported cases has been remarkably uniform and with the recognition of mild

and merely serologically recognized cases has remained around 18 to 0 per cent As a rule the age groups forty to sixty are particularly liable to fatal infections

GEOGRAPHICAL DISTRIBUTION

During the pandemic of 19°9–1930 practically every country in Europe the United States Canada Cuba Hawaiian Islands Mexico Salvador Guatemala Brazil Argentina Africa Algeria and Egypt reported cases Despite the vast reservoir of infection in the parrot population of Australia the actual number of human cases was less than a dozen with only one death This low incidence is probably attributable to the low mammalian pathogenicity of the viruses involved However recent experience with pigeon and fulmar ornithosis amply attests to the possibility that occasionally strains of unusual infectiousness may be encountered Thus psittacosis or orninthosis may be met by physicians in any part of the world Pigeon ornithosis has been conclusively demonstrated by Coles in Pretoria South Africa and by Andrew and Mills in Great Britain It is apparent therefore that in every part of the world these infections may become a diagnostic problem

PATHOLOGY

Psittacosis or ornithosis in man reveals at autopsy the changes characteristic of general septicemia with an inflammatory condition of the lungs which is peculiar and characteristic Consolidation does not conform to that seen in the classic lobar pneumonia or the influenzal pneumonia of 1918 Although grossly lobar the uncomplicated process is lobular in distribution and not markedly related to the bronchioles All stages of congestion edema and hepatization can be observed in the vesicles which are filled with different exudates largely consisting of monocytes and epithelial cells Interstitial infiltration due to lymphocytes and monocytes and to necrosis of the septa may be seen *M multiforme* is found in the epithelial cells and monocytes Pleural reactions are rare There are usually signs of inflammation in the pharynx larynx and trachea particularly in cases complicated by secondary bacterial infection Regional lymphadenopathy shows phagocytic activity in the sinuses The enlarged and soft spleen shows congestion and proliferation of fixed and free phagocytes Parenchymatous degeneration is noted in liver kidneys and myocardium focal necrosis and hyperplasia of the endothelia particularly increased activity of the Kupffer cells are noteworthy Hemorrhages and demyelation in the brain cord and membranes suggestive of cerebral purpura are often present (Sprunt and Berry) The gastro intestinal tract is remarkably free from any severe lesions (Lillie)

SYMPTOMATOLOGY

Onset The first symptoms of the disease are often vague consisting of headache and backache malaise vague pains in the limbs abdominal distention anorexia nausea and vomiting thirst excessive sweating and photophobia

In some cases the onset is gradual and insidious while in others it is fairly acute chilliness and rigors forcing the patient to bed within a few hours Simultaneously with the rise of the temperature the fauces and soft palate are red and congested and sometimes covered with a yellowish exudate In a few instances the tongue may be dry chalky white the edges red and sore Moderate epistaxis is an early symptom but the epistaxis may become more profuse in the second week Another fairly constant feature of the disease is an intense throbbing pressing usually frontal or occipital *headache* This is one of the most unpleasant symptoms since little or no relief is obtained from the usual analgesics Aggravated by paroxysms of coughing it is frequently the cause of sleepless nights Common early features are generalized aches and pains which are apt to localize in the lumbar region

Fever In all cases that have been carefully studied from their incipiency rise of temperature was gradual and stepladder like similar to that of typhoid fever but many patients when seen for the first time often have a temperature of 39 5 C (103 1 F) In these instances an ambulatory period cannot be excluded with certainty but is indicated by the unduly high titer of antibodies in the serum on the supposed eighth day after the onset With the exception of the very mild abortive infection the temperature maintains itself at a high level with only slight morning remissions Occasionally an intermittent type of fever curve has been observed Toward the end of the second or third week it may fall by lysis only in exceptional instances does it fall by crisis During convalescence the temperature may be subnormal In severe usually fatal infections the fever remains high throughout however deaths have occurred after the temperature has returned to normal

Respiratory Tract Pulmonary involvement except in ambulatory or rudimentary cases is a characteristic feature manifested by its objective signs which may be slight and not by its symptoms Moreover every observer has noted the rapidity with which these signs change As a rule the severity of the disease is definitely associated with the degree of lung involvement which to some extent is the determining factor in the development of the toxemia When the involvement is small the patient is not very ill

Toward the end of the first week of the illness a few crepitations may be heard at the base of one or both lungs and rhonchi may be sounded at the apices or scattered throughout the lung Percussion may be slightly impaired and a small area of consolidation may be manifest by dullness Bronchial breathing appears usually near the angle of one scapula Within the next few days similar signs of patchy infiltration are found in other parts of one or both lungs Roentgenologic examinations clearly show this *creeping wandering* type of pneumonia or pneumonitis The primary patch may be small but it migrates along from one part of the lobe to another while the areas previously involved clear up Finally it apparently finds a definite place where it remains for a long period even during convalescence before resolution takes place This is indicated by the return of the percussion note to normal and by numerous moist sounds In the x ray films the first circular homogeneous

density that appears usually at the base of the left lower lobe differs from the usual pneumonic consolidations It is not mottled as in bronchopneumonia and is less opaque than in lobar pneumonia while it differs in its contours from a typical infarct

One of the most remarkable features of the disease is the *frequent absence of rapid or deep breathing* even when the physical signs in the lung indicate progressive and wide focal involvement In fatal cases the picture may ultimately resemble lobar pneumonia with rather rapid but shallow breathing of the tachypneic type Despite the rapid rate real respiratory distress is not noticeable The patients lie flat in bed complaining of headache and cough but never of difficulty in breathing *Cyanosis* is often marked in fatal cases but it does not compare in intensity with that seen in the influenza epidemic of 1918

A slight irritating dry *cough* may increase to varying intensities until painful paroxysms leave the patient exhausted Even in the presence of extensive lung signs cough may be an insignificant symptom or may even be absent throughout the illness The *sputum* as a rule is very scanty and in some cases is completely absent This paucity of sputum entirely out of proportion to the amount the lung signs would lead one to expect suggested the designation of *sputumless or non productive pneumonia* When the consolidation is extensive cough and expectoration of rusty sputum have been observed However the sputum is usually mucoid it may be mucopurulent or frankly purulent while in rare instances it is freely mixed with bright blood Secondary involvement of the bronchial tree produces copious sputa with an abundance of streptococci micrococci even pneumococci and often staphylococci *The latter organism* is sometimes the cause of the secondary fulminating staphylococcic pneumonias

Cardiovascular System Another characteristic feature of the disease is the relative slowness of the pulse it is definitely below 100 often between 80 and 90 in spite of the fact that the temperature may rise to 39 5 C (103 1 F) In most cases it persists throughout the illness but in those with extensive involvement of the lungs and in nearly all fatal cases circulatory collapse with rapid feeble pulse and low blood pressure is common During convalescence the pulse may suddenly rise and become irregular

Nervous System Insomnia of varying degrees irritability and restlessness are not infrequent during the first week and are followed in the second week by a typhoid state This toxemia is entirely out of proportion to the physical signs Stuporous appearance and apathy may be followed by involuntary movements tremors delirium or inertia and apathy not explained by the exhaustion and semicoma Occasionally diminished reflexes and dilation of the pupils are noted The spinal fluid shows no chemical or cytologic changes Complaints concerning disturbance in vision and hearing are not uncommon An immobility of the face may give the impression of parkinsonism Facial neuralgias even paralyses have been reported

Gastro Intestinal Symptoms Nausea and vomiting are early symptoms while *anorexia* and *constipation* are almost the rule and continue throughout the illness Abdominal distention and meteorism are prominent features of the disease when they are not overshadowed by severe pulmonary involvement Occasionally however patients suffer from bouts of diarrhea without consti pation Needless to emphasize the pea soup appearance of the stool together with the pyrexia slow pulse and lethargy present many similarities to typhoid fever

The *liver* may descend one to two finger breadths below the costal margin The *spleen* is as a rule not palpable except in some of the fatal cases There is no evidence of acute nephritis albuminuria is not infrequent and inconti nence occurs Skin lesions resembling rose spots have been reported by Hutchinson Rowlands and Simpson Likewise massive lamellar desquamation and herpes labialis may be present Inflammation of the parotid has been mentioned

Blood Absence of leukocytosis at the beginning is noteworthy while leuko penia is present in about one fourth of the cases During the height of the dis ease a distinct shift to the left of the neutrophils is accompanied by a distinct fall in lymphocytes With general improvement a normal distribution rapidly establishes itself The sedimentation time of the blood cells is definitely acceler ated at the beginning of the illness

Mild and Inapparent Infections In the course of epidemiologic investiga tion Sturdee and Scott Meyer and others saw cases with very mild transitory symptoms and a duration of from two to five days Serologic examinations of persons particularly members of family groups who had been in contact with the same parrots or pigeons responsible for clinical illness of others revealed the presence of antibodies indicative of subclinical inapparent infection In all probability these forms are not infrequent in view of the variable sus ceptibility of man to the psittacosis or ornithosis viruses

COMPLICATIONS AND SEQUELAE

Convalescence in the severer cases is always slow and is frequently inter rupted by relapses but ultimately the recovery appears complete A chronic state has not been observed although there is ample evidence that the infec tive agent may persist in the organs of the body Not only have the complement fixing antibodies of several patients remained at a high titer for years but in two recent observations the same symptoms only much milder and of shorter duration have reappeared at intervals of from four to six years after the first attack In one case the psittacosis virus was isolated from the blood stream In the course of their occupational activities both patients had occasional op portunities to be exposed again to the virus but the circumstantial evidence interprets these second infections as relapses

As sequelae postinfectious myocarditis causing tachycardia and palpitation may be mentioned Thromboses of the femoral veins and during con

valescence a cerebral accident have been seen in one of the recent cases A common cause of death appears to be pulmonary thrombosis

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Definite as is the clinical entity of psittacosis of man its certain diagnosis may nevertheless in any single case and at any one stage of such a case offer considerable difficulty The clinical manifestations are not sufficiently characteristic to permit a diagnosis to be formed from them alone in an isolated case (Sacquépée) Attention has already been called to the very close resemblance of psittacosis to typhoid fever but in typhoid fever the pulmonary symptoms and signs are comparatively slight as compared with those of psittacosis The spleen is palpable in typhoid fever while this is very rarely the case in psittacosis With the aid of blood cultures and agglutination tests the differential diagnosis may be readily established On the other hand influenza and atypical pneumonia are unquestionably the diseases most difficult to differentiate from psittacosis The presence of other cases at the same time and the more rapid onset with more definite symptoms referable to the respiratory tract and roentgenologic observations of the lung may help to differentiate the two diseases A history of association with birds predisposes to a diagnosis of psittacosis although relatively recently cases of influenza or so-called atypical pneumonias with no definite history of avian exposure were ultimately diagnosed as psittacosis or ornithosis Likewise more recent facts contradict the observation that the endemic incidence person-to-person type of spread prevails in influenza only

The *laboratory diagnosis of psittacosis or ornithosis* takes considerable time and exposes the workers to the risk of infection Inoculation of mice with citrated blood collected during the first five days of the illness or with sputum specimens when they are obtainable may ultimately decide the diagnosis although merely in retrospect The complement fixation test originally developed by Bedson and now carried out with boiled tissue culture antigens (Meyer Eddie and Yanamura) furnishes strongly suggestive evidence early in the course of the infection An active phase serum in a dilution of 1 8 on the tenth day will give a strongly positive reaction which will rapidly rise to 1 64 and higher on the fifteenth day of the disease These reactions may be considered specific provided the serum is Wassermann negative and provided the patient is not suffering from an apparent or inapparent infection with the virus of lymphogranuloma venereum

PROGNOSIS

The age of the patient is usually a deciding factor with one exception no deaths in the age group under thirty years have been reported Although the majority of fatal issues occur between the tenth and fifteenth days a thrombosis or embolus extension of the pulmonary process a secondary bacterial infection or a sudden circulatory collapse may decide the ultimate outcome in the second or third week As long as the pulse remains below 100 the prog

nosis is good Marked involvement of the nervous system is always a concomitant of a dangerous illness In general the prognosis of psittacosis or ornithosis is always difficult

TREATMENT

Symptomatic treatment and careful nursing should be conducted along lines similar to those used in typhoid fever Isolation in a quiet environment is imperative in order to reduce the risk of person to-person transmissions

The matter of proper nourishment is important frequent small feedings are indicated Fluids should be given freely for adults from 3 000 to 4 000 cc a day Tepid sponge baths for the reduction of the temperature and for the improvement of the patient s well being are always indicated An ice cap to the head is most agreeable and is sometimes efficacious in reducing fever Needless to emphasize the delirious patient requires particular attention since in his delirium he may get out of bed and do himself some injury Insomnia may be relieved with barbiturates Constipation may be relieved with mineral oil and citrate of magnesia likewise soapsuds enemas are recommended For the treatment of headaches codeine is most useful The administration of expectorant drugs is indicated only when specimens of sputum are desired for laboratory diagnosis The treatment of pneumonia has followed the recognized procedures of recent years administration of oxygen in cyanosis and dyspnea Digitalis has been employed freely but the results are difficult to evaluate The immediate results achieved in relieving the leukopenia with liver or leukocytic extract have been dramatic but it is too early to recommend the general use of these agents Intravenous administration of glucose or hypertonic salt solutions has been beneficial Blood transfusions have also been of value in treatment

Since 1930 the *serum of convalescent* and of normal persons has been used In general doses of from 50 to 200 cc have been administered intramuscularly or intravenously From the limited reports it is difficult to judge objectively the value of this form of therapy Specific neutralizing antibodies are rarely present and the nature of the immunity mechanism in psittacosis is not clearly understood At least in animal experiments human convalescent serum exerted no curative effect On the other hand there is encouraging evidence in favor of hyperimmune animal serums but these still await trial and evaluation

There is no experimental proof that any of the *sulfanilamide preparations* is of value (Meyer and Eddie Rudd and Burnet) whereas according to Mauer trypaflavine has been found to be remarkably effective No observations on man are available

PROPHYLAXIS

Cage birds are so genuinely loved that it is doubtless useless to preach to people as a paramount prophylactic measure the exclusion of parrots love birds and the like from homes Health authorities particularly in California are making strenuous efforts to create and to maintain a parakeet

breeding and distributing industry free from psittacosis and the importations of exotic parrots are subject to careful control But the complete success of these measures offers great difficulties In the light of the recognition that pigeon lofts and the wild parrot population of tropical countries are potent sources of ornithosis or psittacosis these difficulties by comparison appear ephemeral *Prophylactic measures* must be directed toward preventing the transmission of *infections* from person to person Patients should be kept in isolation rooms in which air currents are reduced to a minimum and protective measures should be taken to avoid the escape of air into the wards and halls of the hospital or the home Nurses should wear rubber gloves and masks preferably of the cellophane type

Since Rivers and Schwentker have actively immunized several laboratory workers with living virus the possible danger in creating carriers by this method has been recognized Consequently the procedure has not been used in the protection of persons particularly exposed to the risk of psittacosis

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CHAPTER XXXVII

SMALLPOX

ROBERT F PARKER

SMALLPOX (VARIOLA) IS A CONTAGIOUS DISEASE CAUSED BY infection with a specific virus It has an average incubation period of about ten days (range of from eight to twenty one) which is followed by the abrupt development of the symptoms of a general infection As these symptoms begin to subside in from three to five days a specific exanthem appears One attack ordinarily confers life long immunity

HISTORICAL NOTE

Smallpox was early recognized as a specific disease It was vividly described by Rhazes (850–930) although unmistakable references to it occur in the earliest medical writings Present throughout the known world it flared up periodically in devastating epidemics which were apparently of frequent occurrence although only the most severe were considered worthy of special note Because of its contagious character it was primarily a disease of childhood and few escaped infection With the artificial inoculation of mild strains (variolation) and particularly with the introduction of vaccination by Jenner the incidence and severity of the disease have diminished so that it is now rare in much of the world

ETIOLOGY AND EPIDEMIOLOGY

The etiologic agent is a virus which in common with other members of this group of pathogens is not cultivable on artificial media although it can be maintained in explanted tissues and by the transmission of disease to susceptible animals The disease is highly contagious and is transmitted by direct contact with infected materials (the exanthematous lesions contain virus in high concentration) or by droplet infection which is the more important method of dissemination The virus is world wide in its distribution but the actual prevalence of disease is governed to a large extent by the degree of immunity which is maintained in a community by vaccination For this reason it is generally much more prevalent in rural than in urban areas and among backward peoples than among those in whom the sanitary conscience is

highly developed At the present time it is of considerable importance in India as well as in West Africa and central and northern South America About 1 000 cases a year are reported in the United States There are almost certainly several distinct strains of the virus which give rise to smallpox in varying degrees of severity The milder varieties from time to time have been considered distinct diseases and been given such names as alastrim amaas Cuban itch Philippine itch Kaffir milkpox and so forth There is good evidence to prove that attack by one of these mild strains confers immunity against other strains of the variolous virus Whether more virulent strains may develop from them is not now known with certainty

PATHOLOGY

The essential element in the lesions of smallpox is a ballooning of the infected cells (within which masses of virus may often be demonstrated by appropriate means) followed by focal necrosis and the usual inflammatory response to the necrotic tissue The characteristic exanthem is due to the fact that cells of the rete malpighii in the skin are particularly suceptible to infection the ballooning of the cells and focal necrosis giving rise to the typical pock which is usually multilocular Infection is not however limited to the skin and similar lesions may be found widely distributed in the viscera in fatal cases modified of course by the various locations in which they occur Intranuclear and intracytoplasmic inclusions occur in many cells particularly in those of the skin and are highly characteristic of variolous infection

SYMPTOMATOLOGY

After exposure to infection there is an incubation period of about ten days (sometimes as short as eight days and rarely as long as twenty-one) during which there are no symptoms The onset is usually rather abrupt often with a chill followed by high fever The symptoms at this time are those of invasion by a pathogen causing a general infectious disease and do not usually permit the making of a definite diagnosis There is malaise with general muscular aching headache and very commonly severe lumbar pain This latter symptom when present may indicate the true nature of the disease for it is more severe than in almost any disease save dengue Vomiting is not infrequent and may be severe The fever at this time is usually high (103 to 104 F) and fairly well sustained After three to five days the fever abates the symptoms subside and the patient congratulates himself upon his recovery for in a mild case he may be entirely free of symptoms It is at about this time however that the specific eruption usually makes its appearance

The eruption has a predilection for those parts of the body exposed to mild trauma and it is usually first seen therefore on the backs of the wrists and the forehead as well as the palms and the soles It quickly spreads to the arms the face and the thorax and is usually least severe on the abdomen and thighs A pronounced local increase in severity may be produced if the skin is irritated as with a coarse bandage at the time just preceding the appearance

of the eruption This type of bandage was once used as a means of drawing the eruption from the face but the only actual result was an increase in severity of the exanthem The lesions appear first as macules which quickly progress to papules that have a diameter of from 2 to 4 mm These are fairly deeply embedded in the skin and are surrounded by infiltration in the deeper layers factors which contribute to the shotty feel on palpation Within five or six days each lesion is seen to have become a pustule characteristically multi ocular containing a turbid fluid As development progresses each pustule tends to develop a central depression (umbilication) progressive desicca tion occurs and from each discrete lesion finally separates a small seed representing the dried pustule These contain virus in high concentration in a menstruum which tends to preserve the virus from the adverse effects of physical agents The patient obviously remains a source of contagion until the last scab has separated

At the time of pustulation invasion of the lesions by skin bacteria usually takes place so that each becomes a tiny abscess If the eruption is sufficiently extensive this leads to a second period of fever which subsides as the lesions heal and dry up

COMPLICATIONS

The most common complications of smallpox are *laryngitis* which may produce serious edema *bronchitis* and *bronchopneumonia* *Variolous keratitis* is caused by infection of the cornea by the virus *Septicemia* may occur with extensive secondary infection of the cutaneous pustules which is usually due to a hemolytic streptococcus Focal infection of the skin with pyogenic bacteria is frequent *Postinfectious encephalitis* is rarely seen

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The symptoms of the first stage of the disease are not pathognomonic and the illness may readily be confused with others such as *influenza* or *dengue* With the development of the eruption the diagnosis usually becomes clear although other diseases such as *meningococcal infection* characterized by septi cemia and a rash may cause confusion *Measles* may cause confusion but usu ally does not have the long pre eruptive course and the rash is usually differ ently distributed *Chickenpox* is probably the source of most confusion How ever the shortness of the pre eruptive stage in chickenpox the polymorphous character of the rash and its central distribution as well as the superficial vesicular character of the lesions are usually sufficient for diagnosis The his tory of vaccination is very useful in excluding smallpox *Syphilis* with a sec ondary eruption of pustular type may sometimes have to be excluded

The diagnosis may be established with certainty if laboratory facilities are available by testing the contents of pustules for variolous antigen by either the complement fixation or flocculation reaction for which specific hyper immune serum should be used The former test which is highly specific may be applied with ease to the contents of a single pustule The virus may be

highly developed At the present time it is of considerable importance in India as well as in West Africa and central and northern South America About 1 000 cases a year are reported in the United States There are almost certainly *several distinct strains of the virus which give rise to smallpox in varying de*grees of severity The milder varieties from time to time have been considered distinct diseases and been given such names as alastrim amaas Cuban itch Philippine itch Kaffir milkpox and so forth There is good evidence to prove that attack by one of these mild strains confers immunity against other strains of the variolous virus Whether more virulent strains may develop from them is not now known with certainty

PATHOLOGY

The essential element in the lesions of smallpox is a ballooning of the in fected cells (within which masses of virus may often be demonstrated by appropriate means) followed by focal necrosis and the usual inflammatory re sponse to the necrotic tissue The characteristic exanthem is due to the fact that cells of the rete malpighii in the skin are particularly *suceptible to infec* tion the ballooning of the cells and focal necrosis giving rise to the typical pock which is usually multilocular Infection is not however limited to the skin and similar lesions may be found widely distributed in the viscera in fatal cases modified of course by the various locations in which they occur Intra nuclear and intracytoplasmic inclusions occur in many cells particularly in those of the skin and are highly characteristic of variolous infection

SYMPTOMATOLOGY

After exposure to infection there is an incubation period of about ten days (sometimes as short as eight days and rarely as long as twenty-one) during which there are no symptoms The onset is usually rather abrupt often with a chill followed by high fever The symptoms at this time are those of inva sion by a pathogen causing a general infectious disease and do not usually permit the making of a definite diagnosis There is malaise with general mus cular aching headache and very commonly severe lumbar pain This latter symptom when present may indicate the true nature of the disease for it is more severe than in almost any disease save dengue Vomiting is not infrequent and may be severe The fever at this time is usually high (103 to 104 F) and fairly well sustained After three to five days the fever abates the symptoms subside and the patient congratulates himself upon his recovery for in a mild case he may be entirely free of symptoms It is at about this time however that the specific eruption usually makes its appearance

The eruption has a predilection for those parts of the body exposed to mild trauma and it is usually first seen therefore on the backs of the wrists and the forehead as well as the palms and the soles It quickly spreads to the arms the face and the *thorax and is usually least severe on the abdomen* and thighs A pronounced local increase in severity may be produced if the skin is irritated as with a coarse bandage at the time just preceding the appearance

opiates Ordinarily the diet need be little restricted It should have however a high carbohydrate content and be easily taken and digested since an adequate food intake is of importance in preventing delirium Of even more importance is the intake of water which should be given in quantities of from 3 to 4 liters a day Usually small servings of thick cereals cream soups and similar dishes at frequent intervals will serve to control the vomiting which sometimes develops If vomiting is persistent glucose must be given subcutaneously or intravenously together with sodium chloride and feeding by mouth may be restricted for a day or so

The salient external characteristic of the disease is the pock Because of the destruction of cutaneous structures which its development involves complete avoidance of pitting is not possible The degree of disfigurement however may be minimized by the exercise of care It is important that the pox should not be molested by the patient To help in this the finger nails should be kept short and flannel mittens should be worn during sleep The head may be fixed with sandbags to prevent rubbing of the face or the pillow during consequent excoriation The itching may be allayed by an antipruritic lotion In a mild eruption this lotion may be one such as 1 per cent phenol in oil or calamine lotion with phenol or menthol If the eruption is severe the application of compresses well moistened with 1 10 000 solution of mercuric chloride will give comfort and assist in preventing secondary infection The patient may sometimes be put in a tub of this solution suitably warmed The application of antiseptic solution to the eyes is frequently recommended with the object of preventing corneal localization It would seem wiser however to avoid local application of this sort unless specifically indicated for fear of actually inducing this complication As the eruption dries the skin should be kept oiled to increase comfort and assist in separation of the crusts

Inasmuch as the secondary fever is thought to be due largely to bacterial infection of the pox it may be well to administer one of the sulfonamide drugs during the eruptive stage particularly if the eruption is extensive One with a wide range of action should be chosen such as sulfathiazole or sulfadiazine and an adequate blood concentration should be maintained

PROPHYLAXIS

While theoretically the dissemination of smallpox in a community could be controlled by rigid isolation of each person suffering from the disease this is not feasible since the unrecognized case escaping the quarantine regulations thwarts all the efforts of the health officer The only practicable method for control therefore consists in isolating all cases which are recognized during the period when they are infectious and rendering the population as a whole immune to the disease At the present time immunity to smallpox can be acquired only as a result of having the disease itself or the related one of cowpox or vaccinia The latter disease which is so mild that it is usually not thought of as an infection confers complete immunity against smallpox In a

differentiated from that of chickenpox by inoculation of the chorio allantoic membranes of developing chick embryos The virus of variola produces infection with discrete lesions but that of chickenpox produces no alteration in the membrane Further tests may be applied to material derived from the infected membrane

PROGNOSIS

The outlook in smallpox depends largely on the strain of virus which is causing infection and mortality varies from less than 1 to 40 per cent It is influenced also by the type of care which is given and the effect which this has on secondary bacterial infection of the skin Bronchopneumonia as a complication offers a serious prognosis

TREATMENT

The therapy of smallpox does not differ from that of any other acute self limited disease It is directed to the general care of the patient the minimization of disfigurement and the prevention of spread of the disease in the community

For the protection of the community it is essential to isolate the patient as soon as the diagnosis is established Although it is easier to do this in a special hospital for infectious diseases all essential precautions can be carried out in the home or in a general hospital if special facilities are not available In any case there is no excuse for the incarceration of patients together with their attendants in dilapidated pesthouses a procedure distinguished by its inefficiency as a control measure as well as by its inhumanity When quarantine regulations are formulated it must be borne in mind that the virus is fairly resistant and that it occurs in high concentration in the exanthematous lesions Those occurring on the oral mucous membranes render the oral and nasopharyngeal secretions highly infective Suitable precautions should be taken therefore to interrupt aerial transmission by droplets and to sterilize all dishes bedclothes and other articles with which the patient comes in contact All attendants should of course have been vaccinated or recently revaccinated with potent vaccine virus

There is no specific treatment for the disease Although it is likely that adequate amounts of immune serum will protect against infection if mixed with the virus before inoculation there is abundant experimental as well as clinical evidence indicating that the serum will have no effect on the disease if it is administered after the appearance of the eruption Except for the eruption which presents specific problems of therapy the symptoms of smallpox are those of an acute general infection and their control does not present any peculiar problem The general muscular pains and malaise which characterize the onset usually are easily controlled by the use of acetylsalicylic acid or acetphenetidine but may be severe enough to require codeine or morphine At the time of appearance of the eruption particularly if this is extensive there is some degree of pain in the skin which may be controlled only with

Public Health Service and is to be employed when calf lymph is used although it may also be employed to insert the bacteria free virus It is performed as follows The skin overlying the insertion of the deltoid is cleansed with soap and water and then with a volatile antiseptic such as acetone or alcohol All traces of soap must be carefully removed and sufficient time allowed for the alcohol to evaporate completely The use of non volatile antiseptics such as tincture of iodine or organic mercurials should be avoided since it is difficult to remove them and if even a small amount remains it may inactivate the virus The content of a capillary tube of lymph is expressed on the skin and several needle punctures are made through the lymph over an area not more than 3 mm (1/8 inch) in diameter To make the punctures the physician should hold the needle almost parallel with the skin of the arm which should be depressed strongly in a direction perpendicular to the length of the needle Several minutes should elapse before the excess lymph is wiped off with a dry pledget of cotton Alternatively after cleansing a short incision 1/ inch in length and going just through the epidermis may be made with a sharp scalpel or with a needle The lymph is expressed from the tube and rubbed into the line of incision with the side of the needle or a sterile applicator The resulting lesion will usually be much larger than that following the multiple puncture method but the degree of immunity is probably not increased by the production of a more extensive local lesion No dressing of the wound is needed although if desired a piece of gauze may be attached to the inside of the clothing to prevent contact with the lesion The use of celluloid guards or other occlusive dressings is highly objectionable

Intradermal inoculation should be practiced only with bacteria free virus since in general the introduction of bacteria into the tissues is not desirable It is true however that the bacteria of vaccine lymph are practically all saprophytes and that the chance of inserting a pathogen such as *Cl tetani* is remote Before inoculation the skin should be prepared as described and the inoculation made very superficially as in a tuberculin or a Schick test It is customary to use a volume of 0 1 cc The area should be wiped with a pledget wet with acetone or alcohol after the needle is withdrawn Since the skin is essentially unbroken by the inoculation and since no pustule develops if it has been properly made no dressing is required either at the time of inoculation or later

Vaccinia in a previously uninoculated person follows a typical course The traumatic reaction at the site of inoculation subsides within a day About the fourth day following dermal inoculation a macule appears which quickly becomes a papule This is deep pink or red firm and occupies an area slightly larger than the area scarified By about the sixth day the papule has developed into a multilocular vesicle This gradually increases in size until the ninth day by which time it is considerably elevated above the surface of the skin is filled with a slightly turbid yellowish fluid and has begun to umbilicate The extent of the eruption depends on the area which has been inoculated and this area also governs the size of the scar

community in which vaccination is the rule smallpox cannot occur even though the virus is introduced from without

There are two indications for vaccination It should be carried out as a public health measure with the object of maintaining the general level of immunity in a population at an adequate level All children should be vaccinated during the first year of life and should be revaccinated at the ages of six to fifteen years if this immunity is to be maintained At the time of the first vaccination particularly care should be taken to see that the child is in *good physical condition free from such diseases as eczema or impetigo* as well as any such debilitating disease as diarrhea or respiratory disease The interval between the sixth and twelfth months of life is usually the most desirable

The second indication for vaccination is the possibility of contact with a case of smallpox All persons who might have had any contact even remote with a smallpox patient should be vaccinated or revaccinated as the case may be without regard to previous vaccinal history unless the contact has been extremely remote and a debilitating disease or an extensive dermatitis is present No regard should be paid to the exhibition of the scar of a previous vaccination Immunity is lost at varying rates but the scar is a more or less permanent landmark *Vaccination furthermore should be performed even though* the date of exposure is not known with certainty If it is carried out soon after exposure it may prevent smallpox entirely since the vaccination incubation period is only half that of smallpox If it is later in the incubation period the vaccinia may yet reduce the severity of the more serious disease while if vaccination is performed just before the eruption the variola will have a moderating effect on the vaccinal infection

The material used for vaccination is a suspension of virus which to be of value must be active or alive since the object is to induce vaccinia in the patient In order to insure activity the virus should be as fresh as possible and should be stored at a near freezing temperature The expiration date *given by the manufacturer should be scrupulously observed* The proof of activity of a given lot of vaccine is its ability to produce a take in a high proportion of previously unvaccinated persons The ability to give an immune reaction is not an indication of activity since this may be induced by virus rendered wholly non infectious by heating Virus is usually propagated in two ways (1) The pustules of vaccinia in a calf are harvested at the height of the eruption and suspended in 50 per cent glycerine solution This suspension contains a variable number of saprophytic bacteria ( ) The virus is cultivated in the chick embryo either by inoculating the chorio allantoic membrane of the intact embryo or by using minced tissues suspended in Tyrode s solution Because these preparations are bacteria free they may be inoculated intradermally

The virus may be introduced into the skin by means of multiple needle punctures by light incision of the skin or by intradermal inoculation The method of multiple puncture is advised by the members of the United States

important is *postvaccinal encephalitis* A rare occurrence it appears on the ninth to the thirteenth day after vaccination and is characterized by a stormy course The mortality is approximately 50 per cent but patients who recover usually do so completely Generalized vaccinia occurs rarely with a clinical picture that may be difficult to distinguish from mild smallpox Death from generalized vaccinia has been described but is very rare

As the local lesion evolves it is surrounded by two areas of erythema The first of these to develop is the *aula* an erythematous zone in which there is slight thickening of the skin It appears at the time of vesiculation gradually increases in size for two to three days and has a total diameter of about 15 or 20 mm at the height of the reaction At about the time of pustulation the *area* develops This is a rapidly spreading zone of less intense erythema extending within a day to an area of 60 or 70 mm and often encircling the arm

By the thirteenth or fourteenth day the erythema has faded considerably and a crust has begun to form This crust is usually desquamated by the eighteenth or twentieth day leaving a plum colored base with the characteristic pitting at its periphery

As the eruption reaches its height general symptoms of infection commonly occur The temperature may reach 39 5 C (103 1 F) and there may be nausea vomiting and headache The regional lymph nodes are commonly enlarged and tender These symptoms subside quickly as the lesion begins to heal

The course of vaccinia following intradermal inoculation of cultured virus is similar but if the inoculation is properly performed no vesicle develops There is instead an area of induration about 1 or 2 cm in diameter surrounded by an erythematous zone The skin is not broken at any time and the induration gradually subsides leaving no scar The general reaction is much less and a fever of 38 5 C (101 3 F) is exceptional although the extent of the fever is largely governed by the virulence of the strain used

If vaccinia does not follow the primary inoculation of virus the procedure should be repeated several times Probably the most frequent cause of failure is the use of inactive virus a less common cause is faulty technique in insertion The presence of an inherent resistance to infection while it may occur is very rare

The response to inoculation in a previously vaccinated person is strikingly modified *If the primary vaccination has been performed recently* an *immune* or *immediate* reaction results Within a few hours of the insertion of the virus a macule appears which within one day or at the most two days becomes a typical papule Vesiculation does not occur the papule usually begins to subside by the second or third day and disappears within a week This is largely an allergic reaction and indicates that the individual is immune to vaccinia As immunity is lost various gradations occur between the immune reaction and typical vaccinia Characteristic of partial immunity is the *accelerated* reaction the course of which is that of a vaccinia but the evolution of which is hastened in varying degree The papule appears promptly and the stage of vesiculation may be reached by the third or fourth day with definite regression by the fifth A small scar may result All gradations exist between the immune reaction and typical vaccinia depending on the degree of residual immunity Exact classification of the type of reaction according to a set scheme may be difficult

Various complications of vaccination have been described of these the most

The diagnosis is usually made with ease but a severe infection in an adult may need to be differentiated from smallpox (q v) The uncomplicated disease is associated with practically no mortality death when it occurs almost always being a sequela of skin infections

A possible relationship between chickenpox and herpes zoster has interested a number of investigators It is pointed out that the lesions of the two diseases are strikingly similar and that upon occasion the appearance of the two diseases within a family suggest that one has given rise to another Since neither has been transmitted to the common laboratory animals direct proof is not obtainable However in view of t highly contagious character of chickenpox the scanty evidence for the contagious nature of zoster and the rarity of the association of the two diseases most observers feel that the relationship which has been observed is purely coincidental

There is no specific therapy the general management is that of an acute self limited disease therapy being directed toward relief of symptoms Acetylsalicylic acid and its congeners usually serve to control the acute symptoms when treatment is needed Calamine lotion may be useful in allaying the pruritus which sometimes accompanies a severe eruption and the application of emollient creams to the skin will prevent cracking and abrasion as crusts form over the bases of the skin lesions

The use of convalescent serum with variable success as a prophylactic has been reported If it seems essential to prevent the infection in a debilitated child exposed to risk of infection resort should be to the use of serum collected from individuals who have had the disease within two months and at least 15 cc should be given intramuscularly If given later than the sixth day following exposure it is probably ineffectual

CHAPTER XXXVIII

CHICKENPOX

ROBERT F PARKER

CHICKENPOX (VARICELLA) IS AN INFECTIOUS DISEASE CHARacterized by a papulovesicular eruption which typically develops in crops It is highly contagious and is almost certainly caused by a virus It is usually of gradual onset and the mild symptoms are those of a general infection

The disease was not accurately differentiated from smallpox until 1553 when Ingrassias described the two as separate diseases The term chickenpox is that popularly used to designate the disease in England early in the eighteenth century

The disease is transmissible only to man It is highly contagious and is therefore primarily a disease of childhood (like smallpox) since few who are exposed to infection escape The period during which it is contagious is not *known with certainty but it is thought to be only during the first* week of illness—possibly ten days While the vesicles contain the virus in large quantity the disease is probably transmitted chiefly by means of droplet infection It is world wide in distribution

Since the uncomplicated disease is not accompanied by mortality nothing is known of the internal pathology The characteristic vesicle is very superficially situated in the upper and middle portion of the rete malpighii

The onset of the disease is fairly rapid the period of invasion usually lasting less than twenty four hours The symptoms of the fully developed disease are usually mild consisting of malaise some headache and muscle pains The temperature is usually only moderately elevated The eruption appears soon after symptoms develop it may indeed precede the symptoms Usually two three or more days are required for full development so that lesions may be *found in many* stages of evolution When fully developed the typical lesion is a superficial vesicle 2 or 3 mm in diameter having the appearance of a dew drop Since they are so easily ruptured not many are seen in this stage Symptoms may persist for only a day or so or as long as a week in a severe infection

Complications of the disease are almost wholly those due to infection of the cutaneous lesions by pyogenic bacteria *Postinfectious encephalitis* is rare

in saliva and salivary glands but rarely in other tissues including the blood Virus in saliva is readily destroyed by exposure to desiccation or sunlight In brain tissue the virus is resistant to putrefaction to the action of glycerol 0 5 per cent phenol and certain other substances that are rapidly destructive for many bacteria Although the rabies virus is undoubtedly an intracellular parasite it is by no means certain that the Negri bodies represent intracellular aggregates of the virus A few investigators have attempted to work out the life cycle of the Negri body and have named and listed this structure among the protozoa but these claims like those for successful cultivation of the rabies virus other than in tissue cultures are unconvincing and lack general acceptance

EPIDEMIOLOGY

A wide range of animals is naturally susceptible but since transmission is effected almost solely by biting canines are of greatest importance in maintenance and spread of the infection Dogs are by far the most often incriminated both in transmission of infection to man and to his domesticated animals probably largely because of the freedom accorded dogs In the epidemiology of rabies the importance of the ownerless or stray dog can hardly be overemphasized The disease may remain quiescent for long periods and finally break out in epizootic proportions Cats wolves coyotes skunks and other animals rarely constitute temporary local reservoirs from which man acquires infection Rabid rats are seldom encountered In Trinidad Hurst and Pawan found that the vampire bat was a carrier and capable of transmitting infection both to man and to animals Although possibly human beings are less susceptible than dogs nevertheless it should be remembered that most bites suffered by man are relatively superficial and tend to occur on the extremities At

TABLE VI

RESULTS ON BRAINS TESTED FOR RABIES IN LABORATORIES OF TEXAS STATE DEPARTMENT OF PUBLIC HEALTH 1930 TO 1942 INCLUSIVE

Years	Brains Examined	Brains Positive	Per Cent Positive
1930	1 898	372	9 6
1931	1 478	342	23 1
1932	2 054	536	26 0
1933	2 180	594	23 3
1934	2 472	779	31 5
1935	2 513	831	33 0
1936	2 683	935	38 0
1937	2 825	990	35 0
1938	2 238	610	27 2
1939	2 020	583	23 9
1940	1 538	394	25 6
1941	2 312	671	29 0
1942	2 682	1 075	40 0

CHAPTER XXXIX

RABIES

S W BOHLS AND J V IRONS

OF ALL DISEASES OF MAN NONE IS LOOKED UPON WITH MORE horror than hydrophobia It is an acute infectious disease which is transmitted by the bite or through exposure of an injured nerve as in a cut open sore or abrasion of the skin or mucous membranes to the saliva of a rabid animal The causative agent is a filterable virus The incubation period in rabies averages from six to eight weeks but varies considerably depending on the location and severity of the bite The main symptoms consist of a premonitory or prodromal stage hyperirritability and paralysis followed by death

HISTORICAL NOTE

The experimental method was applied to rabies by several investigators before 1879 when Galtier artificially inoculated rabbits and observed the resultant dumb or paralytic symptoms It was observed early that by artificial subdural inoculation street virus becomes fixed virus upon subsequent passages Fixed virus not only has a shorter and more constant incubation period by subdural inoculation but also tends to be less infective than street virus by subcutaneous inoculation Pasteur and his co workers took advantage of the relatively long incubation period in the natural infection when they carried out investigations between 1880 and 1888 which culminated in the development of the renowned Pasteur treatment for hydrophobia While Pasteur and his co workers employed attenuated virus in dried cord for vaccine production Fermi Semple and others employed similar virus treated with phenol Several other preparations have also been employed in prophylactic immunization In 1903 Remlinger demonstrated the filterability of the virus while Negri discovered in nerve cells the characteristic inclusion bodies which bear his name

ETIOLOGY

The rabies virus is estimated to be about 125 millimicrons in diameter being somewhat intermediate among the viruses with respect to size Although this virus is particularly associated with nervous tissue it is frequently demonstrable

granules Negri bodies are demonstrated best in the large ganglion cells of the hippocampus or in the purkinje cells of the cerebellum These peculiar structures are more difficult to find in fixed virus infections than in street virus infections

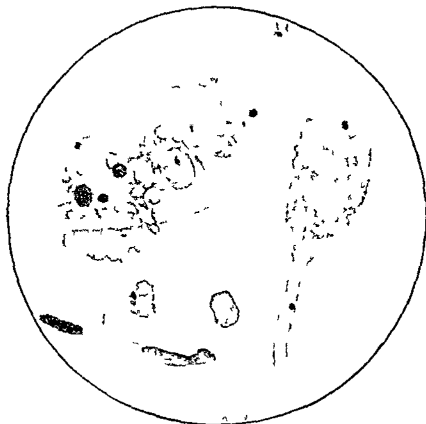


Fig 64 Ammon horn of rabid dog Wilhite Bohls modification of Van Gieson staining method Bausch & Lomb compens oc 12 5 obj apochromat

The nerve cell to the left at the top is largely denuded of dendritic processes but contains five Negri bodies of small or moderate size A fragment at the extreme top contains a small Negri body In the lower part of the field an erythrocyte is partly extruded from a capillary

SYMPTOMATOLOGY

The incubation period in man varies considerably but in most instances it is between five and nine weeks Other than psychic phenomena activated by fear of the disease ordinarily there are no symptoms during the incubation period Rabies in man pursues a course similar to that in the dog except that the furious form in the dog is represented by a spasmodic form in man The

any rate rabies in man is rare compared with its prevalence in dogs and other animals Most human cases occur in young males During the ten year period from 1932 to 1942 593 deaths from rabies were recorded in the United States of which 55 occurred in Texas During 1941 according to Dr John R. Mohler Chief of the Bureau of Animal Industry 7 877 cases of rabies were reported in the United States of which 30 were in man 291 in cats and 6 648 in dogs

Contrary to popular belief rabies is not generally more prevalent during the dog days of July and August Iowa s largest outbreaks of rabies in recent years occurred in the late winter and spring months of 19 5 and 1931 while in Texas possibly the latest and largest outbreak reached a peak in the late winter and spring of 1937 Cyclic changes in incidence over large areas apparently *take place as suggested by tabulations on the occurrence of rabies in* Texas since 1930 (See Table VI)

GEOGRAPHICAL DISTRIBUTION

Rabies is enzootic or epizootic in many parts of the world including most countries both in cold and warm climates A few countries appear to have escaped infection by pursuit of energetic control measures or as a result of fortuitous circumstances Thus apparently rabies has never gained entrance to Australia Rabies has been nearly nonexistent in Denmark Norway and Sweden for forty years or more In the British Isles this virus was excluded during a similar long period of time except for a short time after the first World War The disease tends to be more prevalent in more populous areas and is fairly prevalent in certain areas of the southern part of the United States In recent years Birmingham Alabama was described as the rabies capital of the world but this dubious honor at times could have been claimed by several other localities Hawaii has been very successful in keeping out rabies by enforcement of a relatively long quarantine period (four months) *for dogs presented for entry* Rabies *apparently does not* exist in the Panama Canal zone and is rare in the adjacent Republic of Panama but it is common in Mexico and many parts of Central and South America

PATHOLOGY

Gross pathologic changes are not striking but the brain and meninges are frequently congested and minute areas of softening or hemorrhage may be seen Histologic evidence of hyperemia may be observed in other tissues There are often scattered areas of leukocytic infiltration about the blood vessels or degenerated nerve *cells of the central nervous system which constitute* the rabic tubercles of Babes The greatest significance is attached to the peculiar structures which Negri first observed in nerve cells The Negri bodies (Fig 63) are acidophilic intracytoplasmic inclusion bodies which vary considerably in size shape and number within a cell By the usual staining methods nerve cells are stained blue while the Negri bodies are stained pink or red depending on the methods of staining These structures seldom appear to be homogeneous but rather reveal evidence of an inner structure or at least one or more dark

is accomplished rapidly when satisfactory specimens are available According to Sellers most diagnostic laboratories of the United States employ a modification of van Gieson s stain which was originally an aqueous mixture of methylene blue and rose aniline violet The recent report by Leach corroborates previous determinations of the high degree of specificity of the Negri body test The failure to demonstrate Negri bodies does not necessarily eliminate the possibility of rabies Some of the factors which contribute to failure to demonstrate Negri bodies in brains of rabid animals are too early sacrifice of the animal inability to locate proper tissues in mutilated brains and faulty preparations or hurried examinations According to Leach Negri bodies are apparently more difficult to demonstrate in brains of animals which have been treated with antirabic vaccine The intracerebral inoculation of specially bred mice for detection of Negri bodies requires at least a week longer while the interpretation of results requires special training and experience with viruses

Rabies should be differentiated from drug poisoning tetanus meningitis poliomyelitis encephalitis encephalomyelitis and other infections or disturbances of the central nervous system Differential diagnosis of neurotropic infections is time consuming and laborious and depends on the inoculation of animals and other tests

PROGNOSIS

While relatively few bites by rabid animals result in the appearance of symptoms in man nevertheless when the disease is unmistakably recognized the prognosis is poor Most of the rarely reported instances of recovery in man possibly involved errors in diagnosis Instances of recovery from rabies in dogs have also been reported Death is not the rule in treatment paralysis if one admits that certain instances of treatment paralysis are in reality expressions of the rabies virus

TREATMENT

Treatment is entirely unsatisfactory The patient should be put to bed and should be restrained if necessary Disturbing stimuli which are prone to precipitate spasmodic attacks should be eliminated as far as possible The ordinary sedatives have very little effect in controlling the spasms In rabies as in most virus diseases intracellular existence of the virus apparently presents a barrier against effective action by serum or chemotherapy

PROPHYLAXIS

General Measures Control of rabies depends on enforced restrictions on dogs In view of their nuisance value and the large part which stray dogs have in the spread of rabies the impounding of these homeless creatures is advisable and is possible except in rural areas Annual registration and vaccination of all dogs are desirable measures but difficult to accomplish Temporary quarantine measures as a result of a rabies scare are likely to be only of temporary value but consistent educational measures and regulations regarding reporting of

state of excitement sometimes begins suddenly but more often there are prodromal headaches and discomforts An early characteristic symptom is spasm of the muscles of deglutition and irritability continues until the slightest



FIG 63 Early symptoms of dumb rabies in a rabbit which had been inoculated subdurally with fixed virus five days previously

stimulus such as mention of water or a noise activates spasms of these muscles as well as the muscles of respiration and others Occasionally the salivary secretion becomes abundant and is churned to a froth by spasm of the jaw muscles Delusions and hallucinations develop and anxiety often progresses to a stage of mania Between attacks the patient lies quietly After two or three days, paralysis increases and death occurs shortly The period of excitement sometimes is short and dumb (Fig 63) or else paralytic symptoms may predominate from the start The temperature is elevated particularly during the later course of infection The course of the disease is usually from four to seven days

DIAGNOSIS

Diagnosis of this infection in man or in animals is based on clinical manifestations microscopic examinations animal inoculations or at best a combination of these methods In submitting specimens to the laboratory for diagnosis the clinician should note that fresh unpreserved brain tissue is required this stipulation means that the animal must be killed in a manner designed to avoid injury to the brain Poisoning by strychnine or other methods is inadvisable The whole head should be placed in a water tight container which should be packed in ice and sent by express to the laboratory The use of dry ice is not recommended since freezing may hinder preparation of well stained Negri body films

Direct microscopic examination for Negri bodies is the method of choice and

alcohol and fatigue but otherwise is free to follow his routine duties During the course of immunization local reactions at the sites of inoculation not infrequently occur General symptoms consisting of malaise or elevated temperature sometimes occur

Treatment paralysis is an alarming but rare event occurring during or shortly after the termination of course of immunization The *Fifth Analytical Review of Reports* from the Pasteur Institutes suggests strongly that most instances of treatment paralysis are fixed virus infections Others of these paralytic accidents are probably related to the postencephalitides which occasionally follow measles scarlet fever and smallpox vaccination We hasten to state that the danger of treatment paralysis is not sufficiently great to contraindicate prophylactic immunization of persons who are bitten by rabid animals

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dog bites to the local health authorities are helpful Provisions for prompt prophylactic immunization of all persons needing treatment should be available in every community

When a person is bitten by a dog or other animal the incriminated animal should be apprehended and carefully watched under strict control In the meantime the person s wounds should be cleansed and dressed under a physician s supervision Some authorities have advocated cautery or treatment with fuming nitric acid but these measures have occasioned needless suffering and unnecessary scarring or even disfigurement and are of doubtful value

Prophylactic immunization is likely to be more feasible and also ordinarily permits the delay necessary for observation of the dog or waiting for the diagnosis When suspicion is cast upon a dog a veterinarian should be consulted under whose observation and supervision it is advisable to place the dog Otherwise even if the dog s actions are normal the owner should be impressed with the necessity of keeping his dog under close observation for the following ten days If at the end of a ten day period of observation the dog does not show signs and symptoms of rabies it is reasonably certain that the victim was not inoculated with the rabies virus and the case may be dismissed A difficult situation may arise if the dog escapes and cannot be located or identified or if the brain of an animal is unsuitable for laboratory examination *Under these circumstances common sense measures should be taken* If the wounds are severe and rabid dogs are known recently to have been in the community prophylactic immunization is advisable

Prophylactic Immunization We agree with Webster that both the need for and value of prophylactic immunization oftentimes have been unduly over emphasized The test for evaluation of the immunizing capacity of vaccines developed by Webster and others in recent years has contributed to better immunizing products It is unnecessary to begin treatment while the dog is under observation or while the usual laboratory report is awaited Many situations arise which perplex the physician who realizes that vaccine treatment should not be needlessly administered It should be remembered that the mode of transmission is through the saliva which is infective at most only three or four days before the appearance of definite symptoms Mere contact with an infected animal scratches by a paw or drinking milk from a rabid cow do not indicate need for treatment Bites over clothing often result in nothing more than a faint bruise and when the tooth mark was obviously too superficial to break the skin inoculation could hardly have resulted When diagnosis of rabies is established persons definitely inoculated require prophylactic treatment which must be started as soon as possible particularly when face bites are suffered The Semple phenolized vaccine is widely employed in the United States and is given subcutaneously daily for two weeks Protection is not a certainty but is a reasonable expectation Persons bitten on the neck face or head or suffering deep lacerated wounds over the larger nerve trunks require special attention and more intensive treatment than those with superficial bites on hands or feet During the period of immunization the patient should avoid

Russian and Turkish there was a corresponding rise in incidence with a high peak in the late 90s when the United States Government prohibited further entry of trachomatous individuals Following the enforcement of this regulation together with effective measures of eradication trachoma has been eliminated to a great extent

ETIOLOGY

The disease is infectious and is initiated by a virus The virus varies in size apparently from 0 to 0 5 millimicrons it passes through the usual filters (porcelain diatomaceous or collodion) with difficulty and irregularity it is remarkably frail when it comes in contact with deleterious agents chemical or physical it grows poorly and slowly in the human tissues where the incubation period ranges from a week to a month or more and it has yet to be propagated in any of the artificial or tissue cultural media it possesses a very poor immunizing antigen which accounts for the lack of demonstrable immunity in spontaneous or experimental infection and it is so highly specialized in its activities that it can infect only epithelial cells and only those of the anterior segment of the eye

The epithelial cells of the conjunctiva and cornea contain inclusions or Halberstaedter Prowazek bodies These are best demonstrated in preparations made of cells scraped from the surface of the everted lid and distributed evenly over a slide After fixing with alcohol (merely flooding the slide suffices) the smear is treated with Wright s stain in the manner used in blood smears In general inclusions are found under the oil immersion lens with difficulty and after tedious search The inclusions appear only in the cytoplasm as agglomerations of heterogeneous elements either minute uniform coccoid and pink staining (the *elementary* body) or larger pleomorphic and blue staining (the *initial body*) Typically the body as a whole is found at the edge of the nucleus where it fits somewhat as a cap The composite inclusions in any given case may be entirely of one or the other variety a mixture of both or even the individual components of a single inclusion which may include both elementary and initial bodies

Current opinion supported by strong evidence accepts the inclusion as the infectious agent of trachoma Each inclusion represents a colony of the virus and each elementary or initial body represents an individual virus particle The definite relationship between the infectivity of a given tissue and the presence of inclusion bodies has been presented by the writer

EPIDEMIOLOGY AND GEOGRAPHICAL DISTRIBUTION

While characteristically a rural and familial disease trachoma may and does occur without benefit of either condition Occurring more frequently and more severely in hot dry countries since opportunities for dissemination and secondary infection are greater it is nevertheless found in all climates Its incidence varies tremendously in different countries and probably depends mostly on the efforts made to eradicate the disease and on the co operation given by the

CHAPTER XL

TRACHOMA

I A JULIANELLE

OCCURRING ONLY IN MAN TRACHOMA IS A CHRONIC PROgressive disease of the conjunctiva caused by a virus Characterized by insidious onset following a variable incubation period of several days to a month the infection eventually invades the cornea sometimes involving the adnexa as well and often terminating in partial or complete blindness

HISTORICAL NOTE

The first recorded reference to trachoma is found in the Papyrus Ebers (*ca* 1553 to 1500 B C) with the result that Egypt accurately or erroneously has been given the credit of being the cradle of the disease There is certain evidence however that trachoma goes as far back historically in the Orient particularly in China and Japan Subsequently recognized by both the ancient Greeks and Romans the corneal complications were not realized until the advent of Arabian medicine (fourteenth to fifteenth century A D) when pannus was described as a phase of the infection As far as can be judged at the present time the incidence of trachoma during these centuries was not particularly striking and the sequelae were not severe With Napoleon s invasion of Egypt at the turn of the nineteenth century however the disease began to spread first among the French British and Prussian troops and as they returned to Europe among the civilian populations at home This in turn led to a genuine pandemic when trachoma became particularly widespread Dissemination was eventually controlled not however without leaving important endemic foci of infection

Importation of trachoma to the New World was accomplished so surreptitiously that no adequate explanation of its occurrence exists While considered by some authorities as a contribution of the Spanish conquistadors to the Indians others believe that the disease is of more recent origin Careful analysis of the literature in this regard suggests that trachoma among the Indians is relatively modern probably introduced by the later white settlers As the type of immigrant changed to predominantly Italian Austrian Slavic

SYMPTOMATOLOGY

Occasionally initiated by an acute onset trachoma more typically manifests itself with slowly developing insidious and even negligible symptoms giving rise to bilateral or much less frequently to monocular disease The process is characterized by hypertrophy of the lymphoid tissue which takes the form of follicles (vesicular appearance) or tiny papillae (red velvety appearance) or a combination of both Later follicles may be encountered on the bulbar conjunctiva caruncle and even on the cornea Within a month (as judged by about 98 per cent of all cases) the process penetrates the cornea in the form of infiltration or clouding and vascularization technically designated as pannus The pannus first appears as a curtain of fine capillary loops directly below the superior sclerocorneal margin The capillaries increase in size and number and invade the different levels of the cornea Eventually the vessels spring from the entire circumference coursing their way centripetally With pannus there is gross thickening of the cornea reduction of local resistance thus inviting ulceration and finally impediment to vision The pannus is the outstanding diagnostic feature of trachoma because even when it is completely inactive the collapsed shrunken vessels are still detectable Because of its curtain like character it is readily distinguishable from other forms of corneal vascularization (i e syphilitic keratitis non trachomatous ulceration burns etc) since in the latter the vessels arise as a few strands stretching to and surrounding the site of irritation in the form of the so called salmon patch or spot

Sooner or later the conjunctival hypertrophy is replaced by scar tissue and the cornea may undergo ulceration with resultant permanent opacities or scarring and therefore corresponding permanent loss of vision The discomforts in the meantime include increased lachrimation sensation of extraneous material under the lids discharge pain and extreme photophobia The resultant disabilities are visual impairment or blindness scarring of the conjunctiva and cornea entropion trichiasis ptosis of the lids symblepharon dacryocystitis (when nasal obstruction is present at the lower end of the tear sac) secondary iritis and others

Clinically trachoma has been divided into a number of stages or types by various investigators The most popular of the classifications is that of MacCallan which presents four stages *Stage I* small follicles with or without generalized subepithelial infiltration and with little if any exudate stage I progresses into *stage II or stage III* in the former there is roughening of the conjunctiva with numerous follicles on both tarsal and retrotarsal tissues (stage IIA) or there may be instead a papillary hypertrophy (stage IIB) In this stage secondary bacterial infection becomes common and discharge is the general rule At this time al o pannus formation is most usually seen to begin In *stage III* absorption of follicles begins with replacement by scar tissue Cicatrization may continue to completion and recovery or more frequently it remains incomplete a condition which explains reversion to stage II by

patients We may adopt MacCallan s presentation of the distribution of trachoma namely that the disease is practically universal in its distribution In some countries there are endemic foci which remain while in others the rate of infection is much higher

Trachoma occurs at all ages including infancy when the intimate contact of infected mother and child particularly promotes conditions for infection The greatest frequency is found during adolescence in fact approximately one half of the total cases of trachoma are distributed within the first two decades of life Conditions such as overcrowding carelessness improper personal hygiene and lack of water are responsible for the dissemination of trachoma No races are completely free of the disease Negroes are not immune The low rate among Negroes in the United States is probably explained by the sharp color line and the resultant lack of sufficient contact between the infected whites and uninfected Negroes

PATHOLOGY

Trachoma is primarily a disease of the epithelium When the infectious agent enters the cell there is proliferation of the epithelium which later degenerates Secondarily subepithelial changes also take place with cicatrization of both tissues ultimately occurring In follicular trachoma there is first a thickening of the epithelium and underlying mucosa with congestion of capillaries and the formation of new vessels At times there may be perivascular infiltration by lymph cells and monocytes and in secondary infection by polymorphonuclear cells With the accumulation of mononuclear elements there is thinning of the surface epithelium and even destruction while the subepithelial tissues become thickened The mononuclear elements agglomerate into follicles which with enlargement undergo central necrosis thus leading to ulceration evacuation and finally cicatrization of epithelium and corium In the papillary form of the disease hypertrophy of the epithelium throws the conjunctiva into folds with corresponding invaginations thus creating the papillae The papillae in turn become engorged with lymphocytes and monocytes and from then on the cycle of development is similar to that accompanying the follicles It must be pointed out however that the histologic changes described briefly are not specific of trachoma A number of stimuli infectious and otherwise are able (by their prolonged irritation) to incite both the follicular and papillary reaction and in rarer conditions even the scar tissue

In the cornea the histologic changes begin at the superior limbus below the epithelium with infiltration of monocytes and lymphocytes At first the epithelium undergoes hyperplasia then destruction with denudation Infiltration penetrates the intralamellar spaces and paves the way for the capillaries which eventually form the pannus The cornea may sometimes show follicles ulceration and scar tissue The changes occurring in the corneal stroma create changes in the transparency of the cornea thus rendering it opaque and so explaining loss of vision

changes No method of treatment or surgery has yet been developed to repair such damage Secondary infection adds greatly to the corneal discomfort and renders the process more resistant to treatment

TREATMENT

The treatment of trachoma offers many difficulties and variations In early trachoma exemplified by folliculosis with minor corneal manifestation grattage (i e scraping of the everted lid after injection of an anesthetic as for example novocaine) is the method of choice Preparatory to operation irrigation with tepid boric acid–saline solution is conducted four times daily for several days with drops of 15 per cent silvol 0 1 5 per cent silver nitrate or a similar cleansing preparation Swelling following the operation is reduced with ice and is treated by daily irrigations and cleansing drops as before until most of the trauma or superficial slough has disappeared the cycle usually requiring about a week Then treatment is continued with silver nitrate per cent introduced with an applicator and followed by immediate irrigation with saline–boric acid mixture After a period of from three to four weeks the silver is discontinued and zinc sulfate 0 to 0 5 per cent is applied by the patient in the form of drops twice a day

If the conjunctivitis is papillary rather than follicular in type grattage is not so satisfactory since scraping removes little material and bleeding and trauma during the operation may be excessive The chemical treatment usually proves to be sufficient As scar tissue begins to form silver may be too painful and irritating in this case the better procedure is to apply copper sulfate either as a pencil or by swabbing with a 10 per cent solution in glycerine followed in either case by irrigation in order to protect the cornea If copper is preferred for home use it is advisable to use a concentration of 0 ° per cent As progress is made the zinc salt is substituted for the copper

Aside from the treatment of the lids there is no satisfactory therapy for the relief of pannus and surgical procedures introduced from time to time have been disappointing and ineffectual Usually the corneal infection improves as the conjunctival subsides With secondary infection it may be desirable to use some of the milder chemical agents such as metaphen optochin zephoran When ulceration is present pain may be great it is better therefore to control the ulcer first This is done by hot packs and atropine It is sometimes necessary to apply atropine in the form of salve massaging it lightly under the lids and even bandaging the eyes immediately afterward if the patient is hospitalized In such cases secretion is usually copious so that daily irrigations are particularly important Some ulcers are decidedly refractory to treatment and require ingenuity in their management drastic treatment such as foreign protein shock or the application of the cautery may be necessary In secondarily infected ulcers it may be helpful to apply sulfathiazole ointment made up in a concentration of 5 per cent

More recently the sulfonamide drugs have been introduced into the therapy of trachoma The choice of drug is not particularly important and oral ad

recrudescence or reinfection *Stage II* is the final stage in which scar tissue is generalized and extends even into the subconjunctival tissues

Exacerbations and residual symptoms are discussed under Prognosis

DIAGNOSIS

Diagnosis must be effected almost entirely on clinical grounds There are at the present time no accurate laboratory methods available for confirmatory diagnosis Inoculation of monkeys or apes (the only susceptible animals) is expensive and the results unreliable since there is tremendous variation in individual susceptibility to the virus Examination for inclusions is helpful only when inclusions are found which is in about 50 per cent of cases selected at random If the inclusion is used as a criterion for diagnosis it must be remembered that frequently the inclusion is not found because it is not plentiful or because after the first six months duration it may have completely disappeared Consequently while its presence indicates trachoma its absence may be of only minor significance

In clinical diagnosis the important symptoms are (1) follicular or papillary hypertrophy of the lids (2) infiltration and vascularization of the cornea and (3) cicatrization In the absence of family history or conclusive exposure the diagnosis without the latter two signs cannot be made In early conjunctival trachoma follicular or papillary clinical differentiation from other conjunctivitides particularly those associated with chronic infections and allergies may be very difficult At this time however inclusions are most frequently found With appearance of pannus or scar tissue the signs are more characteristic and diagnosis may be made with a certain degree of assurance In any event there are always borderline cases which remain beyond the limits of conclusive diagnosis

PROGNOSIS

The prognosis of trachoma is extremely variable The prime difficulty is the lack of immunity following an attack so that recurrences are common and difficult to prevent Consequently while the infection may be arrested it is not necessarily cured If the disease is detected early and treated properly the patient may recover with little if any permanent damage If scarring of the lids has already set in there may be turning in of the lids (entropion) with *resultant trichiasis a condition which the patient* makes worse by pulling out the irritating eyelashes This however can be corrected by surgical manipulation Occasionally ectropion (eversion of the lids) may result instead of entropion or again the lids may be so drawn as to shorten uncomfortably the axis from external to internal canthus a condition that has to be alleviated by operation (canthoplasty) The unfortunate outcome is damage to the cornea With infiltration and vascularization there is accompanying loss of vision which will improve even if there is no return to normal with treatment But the presence of pits opacities and scars means permanent loss of vision the degree of impairment depending on the extent of the histologic

following Napoleon s expedition into Egypt demonstrate how simple it is for the returning soldiers to start a genuine pandemic

Nationally prophylaxis may be furthered by making trachoma a notifiable disease Routine examinations should be made in infected areas and the populace should be educated in prophylactic measures Field nurses are of great aid in examining the population first selecting all suspects who are later examined by ophthalmologists Internationally the problem is one of exclusion of all visitors and immigrants suffering from trachoma Individuals with inactive or cured trachoma may be admitted as is done in the United States

It may be well to caution against overzealousness in the desire to eradicate trachoma Obviously inactive cases are not infectious More to the point however is the fact that as scar tissue forms and inclusion bodies disappear the condition becomes correspondingly less infectious even though examination reveals definite clinical activity The chief harm in such instances resides not so much in possible dissemination as in recurrence or recrudescence of the former condition when of course infectiousness returns

ministration is far superior to local application Considerable experience by the writer indicates that the sulfonamides are rarely curative they do however produce rapid subjective and objective improvement It seems advisable therefore that some topical agent be simultaneously employed with sulfonamide therapy The drugs should be given on the basis of 1/3 or 1/4 grain per pound of body weight a day the total dosage to be divided into four different portions during the day (i e sufficient to maintain a blood level of from 3 to 5 mg per 100 cc of blood) Because of the occasional toxic reactions of the drugs the patient should be well supervised to avoid harmful effects

In summary then the regimen to be adopted is irrigation with saline-boric acid solution four times daily sulfonamide therapy as suggested grattage whenever indicated topical agents such as silver copper or zinc as outlined in the preceding paragraphs corneal ulceration to be treated as a special problem on discharging the patient self treatment with drops of zinc sulfate or *even copper sulfate if desirable twice daily for excessive irritation* thereafter not due to recrudescence drops of camphor (sodium bicarbonate grains 20 boric acid grains 10 aqua camphorata dram I aqua distilled oz I) are recommended for both soothing and preventive purposes

There are several sequelae of trachoma that require corrective operations but space does not allow of their discussion at this time

PROPHYLAXIS

There are no specific methods of prevention for trachoma Prophylactic immunization with material containing virus has been attempted in the past without success Consequently whatever methods of prevention are employed must necessarily be non specific and general in nature The results of the program for eradication and prevention in the Scandinavian countries England and our own East Coast illustrate convincingly however that such methods may be sufficiently effective The problem resolves itself into a matter of personal hygiene The patient must be educated in the use of individual soap and water and personal towel He must be taught to keep his hands and face clean to avoid rubbing the eyes or wiping away secretion with his fingers substituting instead clean handkerchiefs or cloths (gauze) which are to be boiled or burned after use The patient should not be exposed to dust or if he must work in the dust he should be trained to use dust goggles It is after such work that the camphor drops suggested above offer relief Those individuals who prefer dark glasses must be trained to use them only in bright sunshine Those in immediate contact with the patient must be taught proper methods of avoiding contamination Since trachoma is spread rapidly among school children in areas of endemic foci periodic examinations should be made by a competent ophthalmologist who uses safety measures himself Infected children should be segregated and educated in hygiene and prevention while under treatment

In military prophylaxis conscripts suffering from trachoma should not be accepted for service nor should they be returned home until arrangements have been made for their treatment and future care Examples such as that

Japanese Encephalitis Type B In 19 4 and 19 7 and in several succeeding years outbreaks of a form of encephalitis occurred in Japan but this differed in many respects from the form (Japanese encephalitis type A) already familiar in that country To this was given the name Japanese encephalitis type B

St Louis Encephalitis An epidemic of this disease first appeared in St Louis during the summer months of 1933 but there is evidence that a small outbreak in Paris Illinois in 193 was the same disease

Equine Encephalomyelitis Since it was first identified during an epidemic in horses in the San Joaquin Valley this disease was considered peculiar to these animals In 1932 the suggestion was made that man might be affected and in 1938 it was definitely established that an epidemic in Massachusetts was due to the virus that caused the disease in horses in the eastern states

Russian Encephalitis A distinct form of encephalitis occurred in Russia for the first time in the spring and summer of 1939

ETIOLOGY AND EPIDEMIOLOGY

Von Economo s Disease The etiology has not been established despite the most intensive investigations Persons of all ages are susceptible and although most of the patients are under forty years of age it appears that this is rather a reflection of the proportion of the general population of this age than of the greater susceptibility of this age group During epidemic periods the disease has occurred most frequently in the winter months but during recent years this tendency to seasonal distribution has been less marked Most of the epidemiologic studies report a somewhat greater incidence of the disease among males than females The disease is widely distributed throughout the world Since its etiology is unknown its mode of transmission and factors affecting its spread are also obscure

St Louis Encephalitis This form of encephalitis is caused by a virus found in the central nervous system of fatal cases It produces a fatal infection in mice and a non fatal infection in *Macacus rhesus* monkeys The virus is not transmissible to other animals although it persists for a short time in the brains of guinea pigs and rats and has been reported to have been passed serially in guinea pig brains and in mouse testicles It has been cultivated in tissue culture and on the chorio-allantoic membrane of the developing chick embryo

Evidence has been obtained to prove that the disease was present also in Kansas City in 1933 Virus identical with the St Louis strains was isolated from a fatal case of encephalitis in Kansas City

Persons who have recovered from St Louis encephalitis possess neutralizing and complement fixing antibodies in their serums against St Louis encephalitis virus By demonstrating neutralizing antibodies in the serums of convalescents in Paris Illinois in 1932 in New York City in 1933 and in Kansas City in 1933 investigators deduced that St Louis encephalitis was present in these localities during these years In the late summer and early fall of 1937 another outbreak of encephalitis similar to that of 1933 occurred in St Louis

CHAPTER XLI

EPIDEMIC ENCEPHALITIS

RALPH S MUCKENFUSS

THE NAME EPIDEMIC ENCEPHALITIS REFERS TO A NUMBER of etiologically distinct infections of the central nervous system as well as to an unknown number of such infections of unknown etiology These infec tions are grouped together because of the similarity of their symptomatology and the inflammatory changes produced by them in the central nervous system The diseases which have been grouped as epidemic encephalitis are von Economo s disease or lethargic encephalitis St Louis encephalitis Japanese encephalitis type A Japanese encephalitis type B equine encephalomyelitis eastern type equine encephalomyelitis western type and Russian encephalitis as well as other varieties of equine encephalomyelitis They are all caused by viruses immunologically distinct from each other with the exception of von Economo s disease which is of unknown etiology The incubation period from such meager information as is available is about two weeks for von Economo s disease and from four to twenty one days for St Louis encephalitis In the few instances on record of possible contact infection of Japanese encephalitis type B the incubation period was from two to twenty days

HISTORICAL NOTE

Von Economo s Disease The first of the encephalitic diseases to be recog nized was described by von Economo in 1917 who called it lethargic encephali tis The disease made its appearance in the United States about 1918 when it was observed in New York City Iowa and West Virginia From 1919 to 19 4 epidemics occurred in various parts of the world Since 19 4 however no important outbreaks have appeared and the disease seems to have lost its epidemic character

When the inconstancy of the symptom of lethargy and the epidemic character of the disease were noticed it became apparent that lethargic encephalitis was a misnomer The term epidemic encephalitis was therefore substituted and this appeared suitable until the identification of other forms of encephalitis etiologically unrelated to von Economo s disease made it untenable for obtain ing reliable diagnostic and epidemiologic data

uniformly present in the blood stream of mice in the early stages of infection and has been isolated from the spinal fluid of patients

Several workers consider mosquitoes to be the agents transmitting this disease

Equine Encephalomyelitis The likelihood that in addition to the horse man is also susceptible to the viruses of equine encephalomyelitis was raised in 1930 when an unusual form of encephalitis was observed in three men working with infected horses In 1938 proof was obtained to this effect An epidemic of 46 cases of encephalitis in Massachusetts was definitely attributed to the eastern type of equine encephalomyelitis virus At the same time 29 cases of encephalitis occurred in Saskatchewan from which the western type of equine encephalomyelitis virus was isolated These viruses are immunologically distinct from one another The eastern type causes a more fulminating infection However from an epidemiologic standpoint they are sufficiently similar to be considered jointly Virus of the western type of equine encephalomyelitis was isolated from a fatal case in California from a case in Minnesota and from two fatal infections in laboratory workers Following infection neutralizing antibodies are present in the serum of convalescents

The disease has a predilection for children About two thirds of the cases in the Massachusetts epidemic were in infants and children less than ten years of age The distribution among the sexes was even In the two epidemics observed in man the disease occurred at about the same time in the late summer and early fall of 1938

Birds mosquitoes and the wood tick *Dermacentor andersoni* Stiles have been incriminated as factors in the transmission of the disease Birds have been the only other animals besides horses in which the disease has been observed to occur spontaneously Virus of the eastern type of equine encephalomyelitis was isolated during an epidemic in ring necked pheasants and from a pigeon Recently the western type of equine encephalomyelitis virus was recovered from a naturally infected prairie chicken In addition a wide variety of birds domestic fowl and other animals has been infected experimentally in the laboratory Indirect evidence for the existence of infection in some of these animals is afforded by the finding of neutralizing antibodies against the western type of equine encephalomyelitis virus in the serums of animals residing in areas where human cases of the disease occurred

Eight species of mosquitoes have been shown capable of transmitting the disease under laboratory conditions The most recent evidence for mosquitoes as vectors of the disease is furnished by successful isolation of the western type of equine encephalomyelitis virus from *Culex tarsalis* mosquitoes collected in localities where human cases of encephalitis were observed

The limited seasonal occurrence the sporadic nature of the outbreaks and the absence of infection through contact favor an insect or arachnid vector for the natural transmission of the virus The disease has been transmitted to the gopher or ground squirrel by the infected wood tick *D andersoni* Not only is the tick itself infected with the western type of equine encephalomyelitis

Epidemics of St Louis encephalitis have occurred characteristically in the late summer and early autumn The disease shows no preference as to sex or color The incidence has been higher in the older age groups

The manner of spread of St Louis encephalitis is consistent with that for a disease transmitted by droplet infection and by unrecognized carriers The existence of subclinical infection in man has not been proved However there is indirect evidence that such infection may occur for neutralizing antibodies are present in presumably normal individuals who give no history of exposure to the virus The exact transmission of the disease is nevertheless unknown

Mosquitoes may be factors in the spread of the disease In the 1933 and 1937 outbreaks of St Louis encephalitis cases were concentrated in the vicinity of small streams in areas containing weeds refuse dumps open sewage and ponds all of which are conditions that could favor the breeding and survival of mosquitoes Moreover St Louis encephalitis virus has been isolated from *Culex tarsalis* mosquitoes collected in areas where human encephalitis cases occurred Mice were infected with these mosquitoes by intracerebral injection However transmission of the disease by the bite of mosquitoes is yet to be demonstrated before it can be stated with certainty that mosquitoes are responsible for the spread of St Louis encephalitis

Field meadow and house mice can be infected experimentally indicating that they may be a potential reservoir of St Louis encephalitis virus but there is no record that they harbor the infection spontaneously

Japanese Encephalitis Type B This resembles St Louis encephalitis but differs from it in that its etiologic agent produces more severe lesions in mice and *Macacus rhesus* monkeys It is pathogenic also for sheep whereas St Louis encephalitis virus is not The Japanese encephalitis virus is neutralized by convalescent serum and is immunologically different from the St Louis encephalitis virus and other viruses of the central nervous system There is some evidence that the Japanese encephalitis virus may be somewhat related to St Louis encephalitis virus Serum from two cases of encephalitis in China neutralized both the Japanese and St Louis encephalitis viruses Serum of rabbits immunized against the Japanese encephalitis virus neutralized not only this virus but also St Louis encephalitis virus However despite an occasional cross neutralization the two viruses are readily distinguishable immunologically from each other The virus of Japanese encephalitis type B has been cultivated in tissue culture and on the chorio allantoic membrane of the developing chick embryo It produces the same change on the chorio-allantoic membrane as St Louis encephalitis virus except that it displays a somewhat greater tendency to the formation of necrotic foci

Epidemiologically Japanese encephalitis type B is similar to St Louis encephalitis It occurs in the late summer and early fall reaching its peak in August or September and terminating with the cool weather An epidemic lasts from four to seven weeks The incidence as in St Louis encephalitis increases with age

Unlike St Louis encephalitis virus the Japanese encephalitis virus is

SYMPTOMATOLOGY

The encephalitic diseases are characterized by symptoms occurring in various combinations and sequence

Von Economo s Disease The onset may be either sudden or gradual The acute stage lasts for a few days It is characterized by slight fever dizziness diplopia ocular paralysis headache sometimes and some stiffness of the neck The symptoms of the acute stage of the disease are variable and in about half of the cases are so mild as to pass unnoticed or not to suggest encephalitis The diagnosis of influenza is often made In the lethargic type of encephalitis fever somnolence and ophthalmoplegia are the characteristic symptoms The hyperkinetic type is characterized by the appearance of severe symptoms of motor irritation following an initial stage of fever and excitement The hyper kinetic types may be either the *choreiform* variety where there are involuntary and irregular movements of the automatic associated types or the *myoclonic* variety in which there is marked irregular twitching of muscles or parts of muscles In other types of the diseases emotional disturbances manic and melancholic states mental deterioration and other psychotic manifestations may be the principal features It may be months or even years before the sequelae (chronic stage) make the diagnosis evident The disease may take one of four courses (1) the patient makes a complete recovery (2) the dis ease progresses until death ensues (3) the disease may become arrested leaving a varying amount of permanent disability and (4) the disease progresses with remissions

St Louis Encephalitis The disease is acute and is characterized by fever prominent signs of meningeal irritation and a comparatively short course Some degree of neck rigidity and a positive Kernig s sign are found in the ma jority of cases Abdominal reflexes are ordinarily absent and deep reflexes diminished or absent Tremors of the tongue and lips are frequent and are especially noticeable when the patient tries to speak Symptoms or signs refer able to the eyes are comparatively rare and usually consist of small and slug gish pupils blurred vision or photophobia The clinical course is rather char acteristic The fever continues high for a few days, quite commonly between 40 and 40 6 C (104 and 105 F) and then gradually diminishes in the majority of instances becoming normal in from six to ten days after admission to the hospital Frequently there is a critical drop in the temperature which usually remains at a normal level in uncomplicated cases In a rare instance the temperature remains elevated In fatal cases the temperature is usually above normal until the time of death Somnolence and stupor when present persist until about the time of defervescence and then rapidly disappear as do the other symptoms and physical signs

Japanese Encephalitis Type B The disease is on the whole similar to St Louis encephalitis Meningeal manifestations are more marked than in Jap anese encephalitis type A A delirious or hyperkinetic state is often observed

virus but its offspring are also infected and can pass on the disease as an hereditary infection Thus the wood tick has two important roles in the transmission of the western type of equine encephalomyelitis—as a transmitting agent or vector and as a reservoir host The heightened incidence of the disease during the summer and fall at least in the United States can best be explained by assuming the mosquito to be the transmitting agent at this time the tick being responsible for the maintenance of the virus from year to year and for its transmission to a variety of hosts especially during the early spring

Russian Encephalitis This is a virus disease transmitted by ticks and is pathogenic for white mice and monkeys The disease was first described in 1939 after its appearance in Russia in the spring and summer of that year The etiologic virus was isolated from infected ticks and rodents from the brains of three fatal cases and in one case from the blood taken at the height of infection It has been cultivated in tissue culture and on the chorio allantoic membrane of the developing chick embryo

Neutralizing antibodies are demonstrable in the serums of convalescents The virus is serologically related to but distinguishable from the virus of Japanese encephalitis type B and the virus of St Louis encephalitis

The disease is endemic in forest regions and is limited to people workin in forests It seems to remain confined in the endemic areas and apparently does not spread from them The disease is considered as essentially an infection of rodents which secondarily infects man

PATHOLOGY

It is not possible by pathologic examination to distinguish the various forms of encephalitis The picture is essentially the same as that reported for the cases examined in 1933 in the St Louis encephalitis outbreak

The essential pathologic process as described by McCordock in the Public Health Bulletin No 214 1935 is an acute nonpurulent inflammation of the central nervous system characterized by intense vascular congestion with petechial hemorrhages cellular infiltration of both nervous tissue and meninges with various types of mononuclear cells and evidences of toxic degeneration in the nerve cells

Vascular congestion is the one constant change found in all cases In severe examples of the disease the inflammatory lesions are widespread throughout the brain and cord In milder cases even though the vascular congestion is universal the inflammatory collections of mononuclear cells may be restricted to one portion of the brain and such cellular infiltration is most likely to be found in the pons medulla or midbrain

The intensity of the inflammatory reaction and the extent of degenerative changes in the nerve cells vary In equine encephalomyelitis all of these changes are extremely severe and in the more serious cases the microscopic reaction is so intense as to be readily distinguished from the common types of en cephalitis

predominate except in equine encephalomyelitis when neutrophils seem to be preponderant Sugar and protein are increased

(2) In addition to von Economo s disease St Louis encephalitis and equine encephalomyelitis only have been recognized in the United States St Louis encephalitis and equine encephalomyelitis have occurred in epidemic form while von Economo s disease is now regarded as an endemic disease

(3) For all diseases in which the etiology is known the virus can be isolated from the central nervous system of fatal cases and can be identified

(4) After convalescence neutralizing or complement fixing antibodies may be demonstrated in the serum

(5) Serious sequelae are rather rare after St Louis encephalitis and Japanese encephalitis type B but frequent after von Economo s disease Japanese encephalitis type A equine encephalomyelitis and Russian encephalitis

(6) Identification of equine encephalomyelitis in man may be further facilitated by the knowledge of the existence of a proved epidemic among horses in the locality where the cases are observed in man

(7) Russian encephalitis is tick borne and is associated with persons working in forests Thus far it has been reported only in Russia

PROGNOSIS

The mortality in different epidemics of von Economo s disease varies from 20 to 30 per cent The death rate is low in those from five to forty years of age and increases in those from forty to sixty years old at which age it is highest This increased fatality in the higher age groups is also noted in St Louis encephalitis Japanese encephalitis type B and Russian encephalitis The fatality in St Louis encephalitis is 20 to 30 per cent in Russian encephalitis 30 per cent and higher in Japanese encephalitis type B over 50 per cent In equine encephalomyelitis the fatality is high being 60 per cent in the Massachusetts and 1 per cent in the Saskatchewan outbreak

TREATMENT

The treatment of epidemic encephalitis is symptomatic for all forms of the disease Lumbar puncture relieves headache and sedation may be necessary in some cases Of all the measures introduced the most promising for relieving the incapacitating developments in the chronic stage of von Economo s disease have been the so-called Bulgarian treatment the use of atropine in massive doses and the use of benzedrine sulphate However it is the consensus of opinion that since the symptoms of the disease are so variable and subject to considerable change further trial is necessary before any definite conclusions can be reached

In the Bulgarian treatment a decoction from the root of the belladonna plant in white wine is used The dosage is controlled entirely by clinical observations of the physician and it is quite certain that it cannot be given without exercising the greatest care Panegrossi in Rome starts with an extremely small dose 2-3 cc being given at 11 P M This dose is increased every

while lethargy is the most frequent symptom in Japanese encephalitis type A. Headache sleeplessness and irritability are encountered in many cases Often the psyche is permanently disturbed especially in children

Equine Encephalomyelitis The onset is sudden in infants but in older children and adults symptoms of indisposition may be present for several days before signs of encephalitis are evident Frontal headache and dizziness are the first complaints of older persons Symptoms of encephalitis appear abruptly and are characterized by fever irritability drowsiness cyanosis and convulsions The patient is usually in a semicomatose or comatose condition on admission to the hospital The course of the disease is characterized by continued tremors or muscular twitchings rigidity of the neck is a constant symptom In infants a tense anterior fontanelle is observed Edema about the eyes and in the upper extremities is also noted in infants Cyanosis is marked A high fever from 39 to 40 C (102° to 104 F) *is the rule* with hyperpyrexia common in fatal cases If recovery occurs the fever drops by lysis over four or five days Once the acute stage is passed the patient falls into a coma and the muscles remain more or less rigid for many days Improvement is slow and ultimate return to normal may be the outcome

Russian Encephalitis The disease is characterized by an acute initial high temperature vomiting meningeal and general cerebral phenomena obscured consciousness and frequently by the development of flaccid paresis paralysis and muscle atrophy mostly of the upper limbs brachial girdle and neck

SEQUELAE

Serious sequelae are frequent after von Economo s disease equine encephalomyelitis and Russian encephalitis but rather rare after St Louis encephalitis *and Japanese encephalitis type B Contractures spasticity* mental deterioration and Parkinson s syndrome are particularly characteristic in von Economo s disease Paralyses mental changes and other sequelae attend equine encephalomyelitis Residual organic lesions occurred in about [illegible]0 per cent of those who recovered from Russian encephalitis

DIAGNOSIS

It is not possible to differentiate the different forms of epidemic encephalitis by clinical observations alone Laboratory study is the only means whereby this can be accomplished In addition other forms of encephalitis as *for* example postinfection encephalitis and other infections of the central nervous system which may confuse the clinical picture must be eliminated before the final diagnosis is reached

The following points may aid the physician in differentiating chiefly those diseases for which the etiologic agent is known

(1) Lumbar puncture generally yields a clear fluid under moderately increased pressure Pleocytosis usually about 50 cells in von Economo s disease about 100 to 300 cells in St Louis encephalitis and from 00 to 000 cells in equine encephalomyelitis is present Mononuclear cells generally

PROPHYLAXIS

In the absence of specific immunizing agents prophylaxis must depend on general sanitary measures aimed at isolating patients restricting visiting wearing of masks by attendants and disinfection of linens discharges and dishes In view of the increasing evidence for insect transmission of St Louis encephalitis Japanese encephalitis type B and equine encephalomyelitis screening of houses in infected areas is advisable in conjunction with all other precautionary measures to prevent breeding of mosquitoes Formalinized chick embryo vaccine has been of value in the immunization of horses against equine encephalomyelitis In man this vaccine has been employed in laboratory workers who have been closely exposed to the virus

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day by 1–3 cc until 20 cc are reached The dose is then divided half being given at 11 A M and half at 11 P M Again each dose is increased and finally decreased if necessary until an optimum dose is reached In the absence of hepatic renal or other organic diseases 60 cc a day may be given safely In very serious cases the dose can be increased to 90 cc without any ill effect. A diet which is mainly lactovegetarian improves the effect of the treatment. Alcohol coffee spices and tobacco are forbidden Treatment is contraindicated in patients with lesions of the heart liver and kidneys with poor general health and with marked rigidity due to fibrosis of the muscles In some cases intolerance to the medication is noted Mental disturbances may be aggravated by the treatment

Atropine in the form of an alkaloid has yielded excellent results The drug is administered in gradually increasing doses until an optimum dose has been reached The dosage generally employed begins with 1 minim of a 0 5 per cent atropine solution This is given three times a day It is increased by 1 to 5 minims daily until a dose of 4 minims three times a day is attained This dosage is usually maintained for three days and then the dose is again increased until 8 minims are administered three times a day This dose is usually repeated for three days and then increased until the optimum dose is determined Some physicians prefer tablets to solutions of atropine

The therapeutic effects of treatment with atropine in high dosage have been summarized by Hall The greatest benefit is seen in cases in which the disability arises chiefly from muscular stiffness and excessive flow of saliva. Improvement may also occur in tremor in the frequency of oculogyric attacks, and in various spasmodic symptoms In these however it is less in amount and more variable Cases in which psychotic disability is predominant and parkinsonism is either absent or only slight do not usually show much benefit from this form of treatment Where the psychotic disability is largely secondary to the physical disability removal of the latter by high atropine dosage may be *accompanied by definite improvement in the former Under no* circumstances does the parkinsonian syndrome completely disappear and unless the treatment is maintained and reinforced by suitable environment using the term in the widest sense there is usually a rapid return to the pre existing condition

Benzedrine sulphate used alone or in combination with atropine has yielded favorable results The greatest improvement has been observed in groups receiving both drugs Improvement in both the subjective and objective behavior of the patients took place Drowsiness was relieved tremor was decreased or totally removed muscular rigidity was decreased oculogyric crises were diminished or disappeared The ability of the patient to work was improved and in many cases patients could resume responsibilities that they had been unable to execute for long periods of time The patients experienced a subjective feeling of increased energy There is little information available concerning the dosage used In one report from 5 to 10 mg were given in the morning and as much as 30 mg at noon

PROPHYLAXIS

In the absence of specific immunizing agents prophylaxis must depend on general sanitary measures aimed at isolating patients restricting visiting wearing of masks by attendants and disinfection of linens discharges and dishes In view of the increasing evidence for insect transmission of St Louis encephalitis Japanese encephalitis type B and equine encephalomyelitis screening of houses in infected areas is advisable in conjunction with all other precautionary measures to prevent breeding of mosquitoes Formalinized chick embryo vaccine has been of value in the immunization of horses against equine encephalomyelitis In man this vaccine has been employed in laboratory workers who have been closely exposed to the virus

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CHAPTER XLII

POLIOMYELITIS

W McD HAMMON

POLIOMYELITIS IS AN ACUTE INFECTIOUS DISEASE OF CHILDhood and adolescence that is caused by a filterable virus It occurs occasionally in a classic paralytic form but much more frequently especially in the tropics as a less easily recognized non paralytic type of infection Both forms appear sporadically or in epidemics The principal pathologic lesions are found in the anterior horns of the spinal cord The incubation period varies from a few days to a month but in general it is from one to two weeks

HISTORICAL NOTE

This disease has probably been widely prevalent for many centuries (International Committee Report 1937) but the first recorded outbreaks are those of Badham (1835) in England and Bull (1868) in Norway Heine (1840) in Germany described a group of cases and later Medin (1890) reported cases in Sweden

ETIOLOGY

The etiologic agent is one of the smallest viruses known but it is able to remain viable under a greater range of external environmental conditions than most others of this group It has been transmitted to monkeys by many routes and a few strains have been adapted to passage in cotton rats (Armstrong 1939a Toomey and Takacs 1941) and one strain to Swiss mice (Armstrong 1939b)

EPIDEMIOLOGY

Age distribution of cases as in diphtheria appears to be determined largely by population density contacts and acquisition of immunity through unrecognized infection (Aycock 1934) Placental transmission of antibody accounts in a large part for rarity of infection in infants under six months of age (Aycock and Kramer 1930) Some variation occurs as might be expected in the age distribution of cases from one epidemic to another but in most instances from 50 to 75 per cent of cases occur in children under five years of

age More clinical cases are recognized in males than in females and the case fatality rate is higher in the former Case fatality rates vary widely but usually fall between 5 and 5 per cent The incompleteness of reporting of non paralytic cases affects all rates

Much uncertainty exists as to the most frequent route of infection in man but from the results of animal experiments human inoculations the finding of virus in washings from the nasopharynx from the feces (Kling Wernstedt and Pettersson 1912) from the mucosa of the intestinal tract (Sabin and Ward 1941) from pools of arthropods (principally flies) (Paul Trask *et al* 1941) and on the basis of many epidemiologic observations it seems probable that infection may occur by many routes

In temperate regions the disease appears principally in the late summer and early fall

Very little information is available in respect to the factors which determine individual susceptibility to the paralytic type Draper (193) and others described particular physical characteristics that distinguish susceptible individuals Aycock (1930 1941a) found suggestive differences in the estrogenic urinary excretion of paralyzed persons and indicated that the factor involved is probably hormonal unbalance He also pointed out that susceptibility to the paralytic form is frequently familial in character (1942a) and more recently that pregnancy also may increase susceptibility (1937 1941b) Tonsillectomy has been demonstrated repeatedly to be a predisposing factor (Aycock 1942b)

Geographical Distribution At present there is excellent evidence in the form of serum neutralization surveys and clinical observations to suggest that the virus is world wide in its distribution From the low age group of recognized cases and the demonstration of many healthy carriers it is evident that opportunities for contact with the virus are frequent Although the clinical disease has been recognized in many tropical countries it appears to manifest itself there in the paralytic form much more rarely than in the northern temperate zone Infection rates however as determined by finding viricidal properties in the blood serum of normal persons are equally high in temperate and tropical areas (Aycock 1929 1930)

PATHOLOGY

Only paralytic cases in man have been studied pathologically and in these the fundamental lesion is necrosis of the anterior horn cells of the spinal cord There is in addition a generalized meningeal reaction with perivascular infiltration Mononuclear cells predominate but at an earlier stage many polymorphonuclear cells are present Edema infiltration of leukocytes and microglial proliferation accompany the degeneration of the neurons Neuronophagia is usually a conspicuous feature The white matter of the medulla oblongata pons midbrain and some areas of the cortex usually shows lesions These also occur in other areas of the brain although less constantly Hyperplasia of lymphoid tissue is the most common lesion apart from the central nervous system

SYMPTOMATOLOGY

Many classifications have been suggested for types of clinical manifestations The division of the non paralytic into abortive and preparalytic is generally accepted The former has varying and ill defined symptomatology resembling that of mild respiratory infection or gastro intestinal disturbance with or without fever or of an abrupt severe febrile episode associated with vomiting and other manifestations common to the onset of any acute childhood infection No signs of involvement of meninges or cord appear A preparalytic case has signs of meningeal involvement but does not have paralysis Recovery frequently takes place at this stage Characteristic spinal fluid findings aid one in arriving at this diagnosis but only during an epidemic is it justifiable to do so and even then at a risk of being in error

A paralytic case may proceed in an orderly manner through a prodromal stage similar to that of the abortive case Then with or without a brief remission it may go through the preparalytic and enter the paralytic stage Other patients although less frequently may have no recognized illness until paralysis is suddenly discovered

Prior to the involvement of the nervous system symptoms and signs may be predominantly respiratory (sore throat coryza) or gastro-intestinal (abdominal pain vomiting diarrhea and later constipation) During the preparalytic stage the patient usually complains of headache presents a flushed face is very alert when examined or observed and appears worried and acutely ill If left alone he is usually drowsy The temperature is elevated to 38 5 or 39 C (101 3 or 102 2° F) and occasionally much higher The spine sign is one of the most constant and characteristic findings when asked to sit up the patient pushes himself upright by use of the hands and props himself up by placing his arms behind or beside him An attempt to flex the head and back toward the knees meets with resistance but to a much less degree than that seen in the purulent meningitides Neurologic examination may reveal irregular and changing tendon responses a positive Kernig sign and loss of the superficial abdominal reflexes Just prior to or accompanying the onset of paralysis tremor and muscle pain are frequently noted Pain often persists

When meningeal signs are present the spinal fluid is usually found to be under increased pressure and is almost always clear although containing an increased number of cells

Paralytic forms are of two principal types bulbar or spinal depending on where the nerve cell lesion is localized The spinal type is seen much more frequently but both types may occur together Sometimes the term respiratory type is used and almost all fatalities occur among these patients They may be divided into three groups (1) those with involvement of the medullary breathing centers leading to irregular breathing (2) those with involvement of the pharyngeal muscles leading to difficulty in swallowing and resulting in choking (3) those with involvement of the intercostal muscles and diaphragm

Spinal involvement leads to a segmental type of flaccid paralysis which usually involves one or more extremities first When bulbar involvement occurs difficulties may develop in speech deglutition or respiration and eye muscle involvement or a Bell s palsy may be noted

The duration of any phase of the disease is variable but in general the prodromal phase if present lasts two or three days the preparalytic one or two days and the febrile period of the paralytic stage from one to two days

Recovery may occur at any time In the non fatal bulbar case it is usually more complete than in the spinal type but even in the latter the degree of restoration of muscle function may be surprisingly great Some muscle recovery almost always takes place but many children are left with extensive residual paralysis Relapses occasionally occur two or three months after the original illness and there are a number of well substantiated reports of second paralytic attacks occurring a year or more after a primary infection

Numerous recent studies indicate that in most cases virus persists in the stools for only a few days after the onset but in several instances virus has been shown to persist for two and three months The usual period of required isolation is twenty one days from the onset of illness

COMPLICATIONS AND SEQUELAE

In almost all paralytic cases some degree of permanent paralysis persists If the patients are not properly cared for during the acute stage and occasionally despite what is considered proper treatment contractions and deformities may occur In children growth of long bones is often interfered with and further deformity imbalance and psychologic disturbances result

DIAGNOSIS

The diagnosis of poliomyelitis at any stage is never certain on clinical and clinical laboratory observations alone Since many etiologic agents capable of producing central nervous system disturbances have been recognized and methods for their isolation improved instances have accumulated in which clinical diagnoses have been proved to be in error During an epidemic of a febrile paralytic disease which conforms in epidemic and clinical pattern to poliomyelitis most diagnoses of paralytic cases will be correct but frequent error will be made in diagnosis of the preparalytic form and in the abortive group the errors both of omission and of inclusion will be great When sporadic cases appear as most frequently happens in the tropics the errors of diagnosis will be even greater

Unfortunately the clinical laboratory offers but slight help and help from the special virus laboratory is seldom available and then is very limited Clinical laboratory studies of the blood and urine yield no particularly characteristic or useful findings Spinal fluid examination is helpful once meningeal signs appear but it is useless earlier The total cell count in the spinal fluid generally is found to be from 5 to 500 per cmm with mononuclear cells predominating but an early tap may yield fluid with large numbers of poly

morphonuclear cells The globulin is slightly increased and sugar is usually normal These findings with absence of other changes negative cultures and negative Wassermann reaction aid in ruling out certain of the bacterial and other parasitic meningitides They do not rule out meningism acute aseptic meningitis lymphocytic choriomeningitis and several of the known virus encephalitides

Neutralization tests made on both acute and convalescent serum specimens by use of mice with a strain of virus adapted to these animals hold out some hope of usefulness in diagnosis if the infection is due to a strain with similar antigenic properties (Hammon and Izumi 1942) Strain differences will probably limit the usefulness of any immunologic test (Kessel 1941 Aycock 1941c) The inoculation of monkeys with fecal material or with pharyngeal washings has yielded virus in many instances Inoculation of cord or medulla the wall of the ileum tonsils and occasionally other tissues has also led to the isolation of virus and thereby rendered more probable a specific etiologic diagnosis

DIFFERENTIAL DIAGNOSIS

A patient presenting the more typical type of clinical picture with characteristic spinal fluid changes may be considered to have poliomyelitis or some other central nervous disturbance of a closely related origin But the atypical paralytic and preparalytic cases can be confused with numerous other infections Encephalitic forms of poliomyelitis except by specific laboratory tests (virus neutralization complement fixation etc) cannot be differentiated from other encephalitides Postdiphtheritic paralysis usually comes on much later Syphilis rickets scurvy arthritis osteomyelitis or even fractures in small children and also certain types of neuritis have not infrequently been mistaken for paralysis Atypical meningeal forms of common infectious diseases including influenza and pneumonia also tuberculous meningitis purulent meningitis and trypanosomiasis may be differentiated from non paralytic poliomyelitis by a carefully taken history by physical examination and by the proper spinal fluid tests Tick bite paralysis may be differentiated from poliomyelitis by finding the tick and by noting prompt recovery when it is removed

TREATMENT

The long established orthodox treatment of acute paralytic poliomyelitis is complete rest in bed and careful immobilization of all affected parts No massage or active motion is permitted and only after several weeks when all pain and tenderness have subsided is cautious passive movement instituted this is followed by hydrotherapy massage and supervised active motion and muscle training Permanent paralysis flail joints and deformity are later corrected by braces and surgery

A new method of treating the acute cases the Kenny treatment (Kenny 1941) is now receiving enthusiastic acclaim from several hospitals where trials have been made Muscle spasm it is demonstrated is a constant accompani

ment of the muscular pain If all involved parts with the exception of joints are poulticed energetically and unturingly with blankets wrung out from boil ing water the amount of spasm is decreased and contractures and deformities are prevented It appears probable that relief of spasm in the affected muscle also reduces the degree of permanent paralysis Once spasm is relieved passive movement within the full range of motion that is possible without pain is in stituted several times a day In addition at the same early stage lessons in muscle training involving limited active motion are painstakingly given Much of the paralysis is attributed to alienation during the period of spasm in the opposing muscle By re education during which substitution of muscles is not permitted much of the muscle s use is regained The treatment is time-consuming and requires careful and intelligent nursing care from persons carefully trained in the method It is stated that in proper hands results are excellent patients are more comfortable and the period of disability shortened

Properly controlled tests of serum therapy have failed to demonstrate the advantage of using any kind of serum even in the earliest recognizable stage of the disease but the opinion of clinicians is still divided as to its effectiveness Many drugs have received temporary acclaim but none has proved to be of value in preventing paralysis

During the acute stage proper drainage of the nasopharynx is of the great est importance in the bulbar type with pharyngeal paralysis When involve ment of the respiratory muscles has occurred prompt and intelligent use of some type of mechanical respirator at the first signs of strain or fatigue may be of great value but in cases in which respiratory embarrassment is due to disturbance of the respiratory center the machine can be of no assistance

PROPHYLAXIS

To the present time vaccines have proved to be either ineffective or danger ous coagulating nasal sprays have had their vogue and today no established method of prophylaxis is available A very short period of passive protection probably results from inoculation with a sufficiently large dose of a potent antiserum but in a disease in which exposure is so frequent indeterminable and unpredictable prophylactic serum will probably prove impracticable in most instances Until we know definitely the modes of transmission not too much can be expected in the way of effective environmental control Till then small children should be given the type and degree of protection other than the specific biologic which we might hope to offer them from both measles and typhoid

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CHAPTER XLIII

LYMPHOGRANULOMA VENEREUM

ARTHUR W. GRACE

LYMPHOGRANULOMA VENEREUM, WHICH IS A WIDESPREAD contagious systemic venereal disease of man, is caused by a filterable virus that is also transmissible to some laboratory animals. It is characterized by acute or chronic, often suppurative, inflammation of the inguinal nodes, the anorectal mucosa, the external genitalia, the perineal and perianal areas and occasionally other organs, depending on the portal of entry.

HISTORICAL NOTE

In 1786 John Hunter noted the existence of inguinal buboes which arose without apparent cause and did not respond to mercurial treatment. The first definite description of a lymphogranulomatous entity was given by William Wallace who in 1833 described what would now be regarded as a chronic suppurative case of lymphogranuloma venereum in the inguinal nodes. In 1849 Huguier gave the name "esthiomene" to a group of chronic ulcerative and hypertrophic lesions of the vulvo-anal region. Durand, Nicolas and Favre in 1913 proposed the name lymphogranuloma inguinale for the disease in the erroneous belief that the histologic picture resembled that of Hodgkin's disease or lymphogranulomatosis. No means existed for making an accurate diagnosis of the disease until 19[illegible]5, when Frei introduced the cutaneous test which bears his name.

The etiologic agent of lymphogranuloma venereum was discovered to be a filterable virus by Hellerstrom and Wassén in 1930 following the intracerebral inoculation of certain macacus monkeys with infected human lymph nodes. The transmission of the virus to mice was accomplished by Levaditi and his colleagues in 193[illegible], and to the yolk sac of the developing chick embryo by Rake in 1940. This facilitated investigation of the serologic interrelationship of lymphogranuloma venereum, psittacosis and meningopneumonitis.

ETIOLOGY, EPIDEMIOLOGY AND GEOGRAPHICAL DISTRIBUTION

The virus of lymphogranuloma venereum measures approximately 0.1[illegible]5 to 0.175 millimicron and is filterable through Berkefeld V or Chamberland L3

candles It is transmissible to monkeys mice guinea pigs cats dogs and grows luxuriantly in the yolk sac of the developing chick embryo and also in tissue culture A developmental cycle of the virus closely resembling that of the etiologic agent of psittacosis has been described by Rake Unlike other viruses, the virus of lymphogranuloma venereum is capable of producing pus sometimes in considerable quantities It is a lymphotropic virus and can be demonstrated in the satellite nodes at about the same time that clinical manifestations appear at the portal of entry The pathogenicity of strains for experimental animals is low and little increase in virulence follows successive passage in them The disease is transmitted by sexual intercourse by pederasty by the use of an enema tip in common with a person suffering from anorectal lymphogranuloma and by contact with freshly deposited discharge from active lesions which contain the virus Thus physicians nurses and midwives have been infected accidentally It is not known how long the virus is capable of survival in discharges outside the body The virus has been shown to be absent from the semen (Grace 1941) It is therefore believed that infection of women and of those male homosexuals who adopt the passive role is due to the presence of open lesions on the genitalia of the active male partner Conjugal infections are found and infections of the external genitalia and anorectal mucosa may appear in small children who sleep in the same bed with an infected person The disease appears all over the world particularly in regions where there is a high incidence of gonorrhea and syphilis The inguinal form of lymphogranuloma venereum has long been known in the tropics as climatic bubo

PATHOLOGY

The most characteristic pathologic lesion of lymphogranuloma venereum is found in the affected inguinal nodes It is termed a stellate abscess and consists of a central area of necrosis containing many intact and broken down polymorphonuclear leukocytes This area is surrounded by a zone of macrophages which in turn is enveloped by a layer of lymphocytes There is no caseation nor are any bacteria to be discerned in histologic sections or by cultural methods Giant cells sometimes of the Langhans type are occasionally found There is considerable periglandular fibrosis Confluence of the stellate abscesses leads to the formation of macroscopic pus the volume of which may occasionally be high although a large amount of pus is more often seen in a chancroidal bubo The active virus is present in the involved nodes This histologic picture while most commonly found in lymphogranuloma venereum is not pathognomonic of the disease because it is also found in conditions in which the Frei test is negative The activity of the virus in lymph nodes and channels may close these structures to the drainage of lymph and so lead to the development of elephantiasis in the areas from which this fluid cannot escape This is most commonly seen in the labia majora and scrotum and to a less extent in the labia minora and penis The histologic picture of lymphogranulomatous elephantiasis cannot be differentiated from elephantiasis due to other causes

Tissues other than lymph nodes respond to the presence of the virus of lymphogranuloma venereum by the formation of granulation tissue in whose meshes are to be found collections of polymorphonuclear leukocytes macrophages lymphocytes and plasma cells This reaction is particularly well illustrated when the anorectal mucosa becomes involved and is replaced by granulation tissue In long standing anorectal disease the entire thickness of the bowel wall may be affected Organization of the fibrous elements of the granulation tissue leads to fibrosis of the affected area This may range in degree from a slight localized irregularity of the mucosa to a band which involves all the coats of the bowel over an area of several square inches and which partially or completely occludes the lumen of the anal canal The property of the virus of producing granulation tissue is responsible also for the ulcerating and cicatrizing lesions of the female external genitalia to which the name esthiomène has been applied

The histologic appearance of the primary lesion is commonly that of an intra-epithelial or subepithelial vesicle with an infiltrate consisting of macrophages lymphocytes and some polymorphonuclear leukocytes in the adjacent areas of the corium

The formation of sinuses and fistulas is often associated with lymphogranuloma venereum They are most frequently seen in cases of the anorectal disease in which they appear as rectovaginal and rectovesical fistulas anal fistula and perianal sinuses

SYMPTOMATOLOGY

Discussion of the disease as it affects the inguinal anorectal and genital areas will be presented in that order

The *inguinal disease* begins from one to three weeks after the infecting coitus with unilateral or bilateral tender enlargement of the inguinal nodes The overlying skin is erythematous and sometimes edematous Periglandular fibrosis leads to matting of the involved nodes Constitutional symptoms usually appear in the form of moderate pyrexia chilly sensations and occasionally fleeting joint pains Cases with septic temperature and enlarged liver and spleen have been observed In about one quarter of the cases the primary lesion is present and usually appears as a herpetic vesicle on the shaft of the penis near the coronal sulcus As it produces no subjective symptoms it is often unnoticed by the patient and generally heals spontaneously without leaving any trace Untreated the enlarged nodes may either recede slowly over a period of weeks or may become fluctuant and discharge pus through sinuses in the overlying skin Before the introduction of the sulfonamide drugs such drainage frequently persisted for months or years Since the use of these compounds sinus formation does not occur as frequently and complete cure can be effected in four or five weeks

The *anorectal disease* presents a variety of clinical forms the commonest of which are proctitis with or without stricture anal fistula perirectal abscess and perianal granulation tissue ulceration and abscess Proctitis with stricture

is probably the most frequently encountered of all the lesions of lymphogranuloma venereum It may be preceded by proctitis without stricture but it is usually discovered after the development of stricture In both conditions the earliest manifestation is a sanguineous anal discharge which soon becomes purulent Proctoscopic examination reveals an inflamed anal and lower rectal mucosa which bleeds spontaneously or upon slight trauma and which may be covered with pus In strictured cases a firm band can be felt and seen to encircle the lumen of the bowel Such a band is usually within reach of the examining finger and is often found in the form of a truncated cone with the narrowest portion of the bowel at the apical end proximally Spontaneous arrest of proctitis sometimes takes place slowly over a period of months In such instances the anal discharge ceases and the granulating area in the walls of the bowel becomes fibrosed A similar result is achieved in most cases by the use of the sulfonamide drugs over a period of at least six months

In untreated cases of proctitis the disease slowly progresses as the area and depth of involvement of the bowel wall becomes increased Such cases are often stubbornly chronic Stricture formation begins to be apparent about eleven months after the onset of the proctitis and cases strictured at their discovery show a gradual narrowing of the bowel lumen Colostomy for relief of symptoms of intestinal obstruction is required in about 18 per cent of cases of anorectal lymphogranuloma at an average interval of about seven years after the inception of the disease

The constitutional symptoms which accompany anorectal lymphogranuloma venereum are usually mild and consist chiefly of abdominal cramps anorexia and secondary anemia Arthritis which occurs in about 10 per cent of long standing cases attacks most frequently the shoulder elbow wrist knee and ankle joints Joint destruction does not occur and full function is ultimately restored Hydrops of the affected joint is present Aspirated fluid is bacteriologically sterile and does not contain the lymphogranuloma virus

In the *genital area* the primary lesion commonly vesicular occasionally appears as an ulcer in such cases concomitant chancroidal or syphilitic infection should be suspected Primary lesions are rare in women The female external genitalia however occasionally present as late manifestations ulcerating and cicatrizing areas which lead to deformity and sometimes to elephantiasis of the clitoris labia majora and labia minora Such a condition has been termed esthiomène and may occur with or without rectal stricture Elephantiasis of the male external genitalia is much less common and is more frequently produced by radical extirpation of lymphogranulomatous inguinal nodes than by the direct action of the disease Urethritis is sometimes caused by the virus of lymphogranuloma venereum and is accompanied by a purulent urethral discharge indistinguishable from that produced by the gonococcus no organisms however can be detected in the discharge either by direct smear or upon culture Parinaud s conjunctivitis may also be a lymphogranulomatous manifestation This is a unilateral chronic inflammatory condition of the conjunctiva associated with satellite lymphadenopathy In severe untreated

cases involvement of the cornea occurs with loss of sight Extragenital infections of the tongue with regional lymphadenopathy due to perverted intercourse have been described Cutaneous eruptions mainly of the erythema multiforme type appear occasionally in persons who have the typical lesions of lymphogranuloma venereum and are regarded as manifestations of allergy to the virus

The disease appears in asymptomatic as well as in symptomatic form The former is met with almost exclusively in persons who suffer from or who have suffered from other venereal diseases and is considerably more common than the symptomatic form Individuals apparently cured of the disease as shown by cessation of clinical activity seldom show relapses Such recurrences as do occur are found in the anorectal area where resumption of bloody purulent anal discharge occasionally follows after months of freedom from symptoms There is no evidence of the existence of a carrier state in lymphogranuloma venereum Residual symptoms are found chiefly in the anorectal disease and appear most commonly as anal or rectal stricture anal fistula perirectal abscess and rectovaginal discharge

COMPLICATIONS AND SEQUELAE

The commonest complication of lymphogranuloma venereum is the production of a degree of stenosis of the lower bowel which is sometimes sufficiently severe to warrant the performance of a colostomy In rare instances pus will track to a considerable distance from its source (usually in the anorectal region) to produce perinephritic or subdural abscess

DIAGNOSIS

The diagnosis of lymphogranuloma venereum is made by means of the Frei test which is performed by the intradermal inoculation of Frei antigen The reaction usually becomes positive six weeks after the infecting coitus in the case of the anorectal disease and three weeks after in the inguinal disease and persists for life The original antigen as introduced by Frei was a 20 per cent saline suspension of pus aspirated from an unbroken lymphogranulomatous bubo and inactivated by heating at 60 C for two hours on one day and for one hour on the next day Such material is known as human antigen It has several disadvantages the chief of which are the comparative unavailability of suitable pus the wide range of virus content of pus the possibility of the presence in the pus of disease agents other than the lymphogranuloma virus In order to overcome the drawbacks attendant upon the use of human antigen the brains of mice infected with the virus of lymphogranuloma venereum were employed as antigen in a 13 per cent concentration in saline inactivated by heat in the same way as in the preparation of human antigen The discovery by Rake that the elementary bodies of the lymphogranuloma virus can be obtained in large numbers by growth in the yolk sac of the developing chick embryo has resulted in the production of an antigen which appears to have few if any disadvantages This material known as a yolk sac

antigen is a 1 in 200 saline suspension of the granules of the virus and is practically water clear It is the most sensitive antigen yet devised For the test, 0 1 cc of antigen is injected intradermally and the reaction is observed at forty eight or seventy two hours The appearance of the reacting area is that of a central papule or induration sometimes capped with a vesicle or pustule and surrounded by an erythematous zone The size of the erythematous area is of no diagnostic import The larger papules usually take several weeks to subside A positive Frei reaction in a person who was once lymphogranulomatous demands a careful study of his past history since the latter positive Frei test may be the outcome of an earlier infection with lymphogranuloma venereum and therefore unrelated to the existing clinical manifestations

A complement fixation test for lymphogranuloma venereum was introduced by Rake in 1940 The antigen is a suspension of the granules of the virus grown in the yolk sac of a developing chick embryo It is by means of the complement fixation test that the close serologic interrelationship between the viruses of lymphogranuloma venereum psittacosis and meningopneumonitis has recently been discovered These three viruses are similar in size and appearance in developmental forms and tinctorial characteristics in addition to common or closely related antigenic constituents

The blood count in lymphogranuloma venereum has no diagnostic significance There is moderate leukocytosis with relative polymorphonuclear increase in the acute stage of the disease in the inguinal area and slight secondary anemia in chronic cases of the anorectal disease Urinary changes are unimportant Study of the serum proteins has revealed some interesting facts Gutman showed that in certain cases of lymphogranuloma venereum the total serum protein may reach a level as high as 11 to 12 per cent The increase is due almost entirely to globulin the proportion of which exceeds that of albumin in the serum This reversal of albumin globulin ratio is sometimes indicative of activity At times a parallel appears to exist between the duration of the disease and the degree of hyperproteinemia long standing cases of lymphogranuloma venereum particularly those of proctitis with stricture show the highest figures The significance of hyperproteinemia in lymphogranuloma venereum is unknown

DIFFERENTIAL DIAGNOSIS

Lymphogranuloma venereum must be differentiated from chancroid bubo due to pyogenic lesions of the lower extremities tuberculosis of the inguinal nodes gonorrhea syphilis granuloma inguinale balanitis bubonic plague tularemia carcinoma and tuberculosis of the rectum ulcerative colitis and chronic amebic and bacillary dysentery

Chancroid Hemophilus ducreyi can be demonstrated in 80 per cent of smears obtained from primary chancroid lesions by the use of Unna Pappenheim methyl green pyronin stain The organism is seldom found in pus from unbroken buboes A positive Ito-Reenstierna skin reaction is also obtained in 95 per cent of the cases diagnosed clinically as chancroid There is greater tender

ness of and pus in the chancroidal bubo than in that of lymphogranuloma venereum

Pyogenic lesions of the lower extremities can be easily detected and the pus obtained from the bubo will contain the offending pyogenic bacteria

Tuberculosis of the inguinal nodes is more commonly found in children than in adults The involved node shows the presence of the tubercle bacillus on direct smear or culture or following guinea pig inoculation

Gonorrhea Inguinal adenitis is rarely encountered in a simple infection with the gonococcus When it does occur however there is concomitant urethritis and the existence of the organism in the urethral discharge will establish the diagnosis of gonorrhea

Syphilis Differentiation must be made between Wassermann negative syphilis and non suppurative lymphogranulomatous inguinal nodes The presence of *Treponema pallidum* in material obtained from the node or concomitant primary genital lesion will substantiate the diagnosis of syphilis

Granuloma inguinale Inguinal swellings are seldom found in this disease The early genital lesions of granuloma inguinale may resemble an unusual form of primary sore of lymphogranuloma venereum The presence of Donovan bodies in smears from the freshly cut advancing edge of the granulomatous lesion will establish the diagnosis of granuloma inguinale Esthiomene may occur also in granuloma inguinale

Balanitis There is no test for the diagnosis of this disease which may resemble a primary lymphogranulomatous penile lesion The diagnosis of balanitis can be made only after specific infective agents have been excluded

Bubonic plague will be suspected only in localities where it is endemic or epidemic It is readily diagnosed by the discovery of the plague bacillus in the bubo pus

Tularemia is found most commonly where there is considerable handling of wild rabbit pelts The satellite suppurative adenopathy which follows the development of the primary lesion at the portal of entry of the organism is usually to be found in the axilla a most unusual site for lymphogranuloma venereum The diagnosis of tularemia is established by the presence of *Bact tularense* in the bubo pus

Carcinoma of the rectum The firm stricture with diffuse inflammation and ulceration and bloody purulent anal discharge which is characteristic of lymphogranulomatous proctitis with stricture often leads those unfamiliar with the significance of this picture to a mistaken diagnosis of carcinoma of the rectum It must be remembered that lymphogranuloma venereum and carcinoma can coexist in the lower bowel thus rendering imperative the performance of a biopsy in all cases in which malignancy is suspected

Tuberculosis of the rectum This condition is rarer than anorectal lymphogranuloma from which it may be differentiated by the discovery of the typical architecture or organisms of tuberculosis following histologic examination of a portion of the ulcerated bowel

Ulcerative colitis causes intense inflammatory involvement of the mucosa of the lower bowel and may be accompanied by stricture Differentiation between this condition and lymphogranuloma venereum is difficult It is best attempted by the performance of the Frei test Cases of ulcerative colitis have occasionally been observed which were apparently due to the virus of lymphogranuloma venereum

Chronic amebic and bacillary dysentery The former at times may be distinguished from lymphogranulomatous proctitis by the discovery of *Endamoeba histolytica* in scrapings or culture from the base of the mucosal ulcers or in histologic preparations of the ulcerated mucosa Bacillary dysentery is differentiated by the presence in the blood serum of agglutinins for the specific dysentery bacilli and by positive stool cultures

PROGNOSIS

Lymphogranuloma venereum treated or untreated seldom causes death. The rare fatal cases have usually resulted from the extension of infection from the original site commonly the anorectal area to the perirenal tissues or spinal meninges in other instances the advancing granulomatous process has caused fatal hemorrhage from large vessels The prognosis of cases treated with the sulfonamide drugs is excellent

TREATMENT

A variety of measures were employed for the treatment of lymphogranuloma venereum before the introduction of the sulfonamide drugs The chief of these include injections of Frei antigen or antimony compounds aspiration excision or incision and drainage of buboes performance of colostomy with or without resection of the rectum dilatation of rectal strictures topical application of balsman of peru to areas of ulceration on the external genitalia or anorectal region roentgen rays applied to the groin or rectum and medicated enemas Sulfanilamide (in combination with fuadin) was introduced by Gjuric in 1938 for the treatment of inguinal lymphogranuloma and the use of the drug was extended to cases of the anorectal disease by Shropshear and also by Shaffer and Arnold The good results reported by each of these investigators have since received abundant confirmation Sulfanilamide has been replaced by sulfathiazole because of the lower incidence of toxic reactions obtained with the latter drug Sulfathiazole is administered in a course which consists of 1 5 gm three times daily for two weeks followed immediately by 1 0 gm three times daily for three weeks A single course together with aspiration of frank pus is sufficient for the cure of inguinal lymphogranuloma

The form of the anorectal disease most amenable to sulfonamide therapy is proctitis which unlike lymphogranulomatous adenitis seldom heals spontaneously Cases of short duration without stricture can be completely healed Long standing cases and all cases with stricture require at least one year s therapy with rest periods of from two to three weeks between courses of treatment Surgery has a place in the management of many cases of anorectal lymphogran

uloma particularly in those with anal fistula and perirectal abscesses Surgical procedures should however be preceded and followed by at least one course of sulfathiazole therapy Patterson has recently introduced an operation for use in cases of the anorectal disease which are complicated by proctitis (with or without stricture) and numerous anal fistulas A permanent short pouch colostomy is performed and followed within a few weeks by the stripping of the entire mucosa of the lower segment of the bowel thereby removing the bulk of the disease bearing tissue the fistulas are laid wide open and granulomatous perianal lesions are excised Fibrous stricture is uninfluenced by any form of therapy in the absence of proctitis the lumen of the strictured area may be enlarged by the use of dilators Antimony is valueless in the treatment of lymphogranuloma venereum

PROPHYLAXIS

The most satisfactory measures that can be employed in the prophylaxis of lymphogranuloma venereum are (1) the wearing of a condom during intercourse ( ) thorough washing of the external genitalia and pubis with soap and water immediately after the sexual act and (3) the anointing of the washed parts with 5 per cent sulfathiazole ointment which is allowed to remain in position for several hours No information is available on the prophylactic value of the sulfonamides administered prior to exposure

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SECTION SIX

DISEASES CAUSED BY BACTERIA

CHAPTER XLIV

PLAGUE

GEORGE W. McCOY

PLAGUE IS AN ACUTE SPECIFIC INFECTIOUS OFTEN FATAL disease occurring naturally in many species of rodents from which man sometimes is infected It is caused by a micro-organism *Pasteurella pestis* which usually attacks primarily the lymph nodes or the lungs

There are in man two main clinical types of plague namely the *pneumonic* type sometimes called lung plague and the *bubonic* type in which the infection involves chiefly or primarily the lymphatic structures of the body A third form is recognized the *septicemic* type in which early blood stream invasion is the dominant feature *Carbuncular* and *angionose* forms also are recognized the names of which are sufficiently descriptive An infecting organism of low virulence or a high resistance in the infected persons may result in a very mild form called *pestis minor*

Epidemiologically plague may be classified by source and by mode of transmission

1 Source
   (*a*) Rat origin usually urban (murine)
   (*b*) Wild rodents usually rural (sylvatic)
2 Transmission
   (*a*) Infected animal to man by way of insects usually fleas (bubonic and septicemic)
   (*b*) Man to man by direct contact usually droplet infection (pneumonic)

HISTORICAL NOTE

As with many other diseases the exact date of the first recognition of plague is unknown Some students of the subject regard the passage in Samuel I which refers to a disease in man characterized by *emerods* (buboes?) and existing in conjunction with an epizootic among mice as a reference to bubonic plague There would seem to be no doubt that the epidemic described by Rufus of Ephesus who lived early in the Christian era was plague *Pestilentes bubones maximi letales et acuti qui maxime circa Lybiam et Aegyptium et Syriam observantum* could hardly have been anything else The next great outbreak of

plague that needs to be mentioned occurred about the middle of the fourteenth century and was known as the Black Death This outbreak devastated much of the then known world and deaths were so numerous as to reduce greatly the population of Europe It was in this outbreak that Guy de Chauliac of Avignon (France) clearly recognized the two main clinical types pneumonic and bubonic mentioning that the former was characterized by continuous fever and bloody sputum and by the death of the patient within three days and that the latter was characterized by continuous fever with swelling and abscesses in the palpable glands particularly in the axillary and inguinal regions and was fatal in five days There were outbreaks during later periods that of 1665 usually spoken of as the great plague of London being the most notable

The next great pandemic to which attention must be given began in China in 1894 where it appears to have been confined until 1896 when it spread to India and Europe and thence to other parts of the world The disease reached Hawaii in 1899 and the mainland of America at San Francisco California in 1900 About the same time some South American ports were infected In 1914 it reached New Orleans and in 1920 Galveston and Beaumont Texas Pensacola Florida all ports on the Gulf of Mexico It is to be noted that the disease has never occurred in the Atlantic coast region of the United States The reasons for this are not clear probably several factors operate to prevent its occurrence the most important being the insufficient density of rodent or flea population or both and this in turn may be the result of building practice (affecting rat harborage) which is influenced by climatic conditions

The pandemic that started in China in 1894 was the first to occur since the beginning of the era of bacteriology Investigators took advantage of the opportunity to study the disease by the then relatively new methods of research, and great progress was speedily made In 1894 Kitasato and Yersin working independently discovered the causative organism

In the early part of the twentieth century Verjbitski a Russian worker investigated the relationship between plague in rodents and in man and the role of insects in transmission of the disease This work was followed by the epoch making studies of the Advisory Committee appointed by the Secretary of *State for India the Royal Society and the Lister Institute* usually spoken of as the Indian Plague Commission The studies of this committee established the relationship between rodent plague and the disease in man and the mechanism of transfer from rodent to man by means of the rat flea Their studies also pointed the way to the control of epidemics

ETIOLOGY

Pasteurella pestis the causative agent is an aerobic (though it will multiply under less than atmospheric oxygen) non sporing gram negative coccobacillary organism which grows well on ordinary culture media The disease in man usually can be related to the disease in rodents though it is possible to have

infection in rodents and to have few or no human cases Infection among rodents and from rodents to man depends to some extent on the number and type of the rodent fleas prevalent

Transmission The pneumonic type of plague is conveyed directly from person to person probably by coughing (droplet infection) How the first case in an outbreak of this type of plague originates is not always clear The epidemic may start from a case of the bubonic or septicemic type which has developed a secondary plague pneumonia or by primary infection of the upper respiratory passages of man from an infected rodent subsequent cases in either event being by direct infection from one human being to another

The bubonic type is usually transmitted from rodent to rodent and from rodent to man by the bite of a flea The most common carrier is the *Xenopsylla cheopis* but other fleas are experimentally effective and doubtless sometimes are carriers in nature The flea acquires the infection from a rodent by sucking blood when the animal has a blood stream infection There is evidence that the flea does not act merely as a passive carrier conveying the infection on its biting parts from one host to another but rather that the plague organisms multiply in the flea and are injected into the new host during a subsequent act of feeding *X cheopis* readily bites man The flea acts as a living culture tube the multiplication of the organism taking place in the gastro enteric tract of the parasite There is sometimes obstruction in the anterior part of this tract by masses of the pest bacilli which often results in the early death of the flea When a flea in this blocked condition attempts to feed on a new host there is regurgitation which brings about the injection of plague bacilli into the puncture wound made by its mouth parts

EPIDEMIOLOGY

Plague occurs in both sexes in all races and at all ages but it is comparatively rare in young children Epidemics that were predominantly of the pneumonic type were long thought to be confined to the colder parts of the world but in recent years this type has been found in other areas There have been two small epidemics of this type in the United States both in California one of 14 cases in Oakland in 1919 and one of 33 cases in Los Angeles in 1924 Many epidemics may be a mixture of pneumonic and bubonic cases

The bubonic type depends on a rodent host rat squirrel or other animal and a suitable ectoparasite (flea) vector The common black rat (*Rattus rattus*) the gray or wharf rat (*Rattus norvegicus*) and the white bellied black rat (*Rattus rattus alexandrinus*) are the principal plague carriers in the family of the Muridae

Other rodents that play a role chiefly in sylvatic plague are tarbagans in Asiatic Russia guinea pigs in South America and ground squirrels field rats and prairie dogs in the United States and elsewhere In South Africa several varieties of field rodents have been found infected

Certain climatic conditions are regarded as important in controlling seasonal prevalence In general transmission of rat plague is most likely to occur at

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PATHOLOGY

The pathology of plague of the bubonic type *in man* is usually quite characteristic Usually the body is livid and there may be subcutaneous hemorrhages The primary bubo most frequently found in the groin is composed of a subcutaneous yellowish or blood stained serous exudate overlying and surrounding a much enlarged lymph node or group of nodes that is often embedded in a surrounding hemorrhagic mass On section the node is found to be blood stained and of a cheesy consistency In cases that have survived for a considerable period the node may have been converted into a purulent mass Secondary buboes are found proximal to the primary one and have the same pathologic appearance although in a less advanced stage In some cases the nodes remote from the primary bubo will show similar changes There are often subserous hemorrhages The spleen is much enlarged The liver often presents a yellowish appearance the normal chocolate color being replaced by a mottling due to necrosis Subacute cases often show pyemic like foci in the viscera and lymph nodes

In naturally infected *rodents* the gross pathology differs somewhat according to species In *rats* the bubo is usually discreet hemorrhagic and necrotic The location of the primary bubo in this animal seems to vary in different parts of the world in India most of the buboes are found in the region of the neck while in the United States the groin seems to be the favorite site There is an intense subcutaneous congestion of a dusky red appearance the spleen is much enlarged but firm with well preserved outlines the liver shows fine stippling often there is a clear or blood stained pleural effusion which may be found on either one or both sides Not all rats are to be expected to show all these signs and various combinations of two or more are found

In *squirrels* the bubo is often partially or completely surrounded by a bloody area and is made up of a rather dry somewhat blood stained cheese like content The spleen is very much enlarged quite firm and often shows necrotic foci In squirrels that have survived ten days or longer the lungs are usually involved and then the whole pathology of these animals resembles somewhat that of infection due to the tubercle bacillus (*Mycobacterium tuberculosis*)

In both rats and squirrels if the disease has become subacute or chronic there is a tendency toward the formation of purulent foci in lymph nodes and viscera In squirrels the lesions either acute or chronic are almost indistinguishable from those due to tularemia

The gross lesions of the bubonic type of plague in man and wild rats are very characteristic so much so indeed that often a satisfactory opinion may be rendered on the basis of these lesions alone

In pneumonic plague the process is that of a lobular pneumonia which is said to simulate that found in influenzal pneumonia There are varying degrees of congestion and consolidation The cut surface does not present the granular appearance of lobar pneumonia

temperatures below 26.5 C (79.7 F) Temperatures above 30 C (86 F) result in great reduction or extinction of the infection The prevalence of plague in rodents is the essential condition for an epidemic The epizootic begins before the epidemic and lags after that phase has passed Outbreaks of bubonic plague in man usually are urban and are due to rat infections while scattered cases in rural areas usually are the result of infection from wild rodents This latter type of epizootic and endemic prevalence is often spoken of as sylvatic plague but the term usually refers to the rodent infection rather than to that in man That this type is much less important as a source of human cases is well illustrated by the experience in the western part of the United States Plague of rat origin in San Francisco from 1900 to 1904 resulted in over 100 human cases while in the thirty five years ending in 1941 rural human plague thought to have originated from squirrels and other wild rodents averaged scarcely one case a year

The tenaciousness with which sylvatic and possibly murine plague clings to an area is remarkable For example plague has prevailed among the rats in one of the Hawaiian Islands from 1900 until the present time 1948 and substantially the same may be said of the infection among ground squirrels in California The mode of spread of sylvatic plague from one area to another is not clear doubtless peripheral extension from one rodent colony to another occurs but it has been suggested that isolated foci may develop from transportation of infected fleas or infected rodents through the agency of predatory birds

Probably several factors or a combination of them cause plague epidemics to end naturally Among these are a growing immunity of the rodent population and the loss of virulence of the infecting organism

Plague tends to recur at the same season of the year in any given locality These recurrences are probably governed largely by climatic conditions which influence the number of rodents and fleas and the fate of the infection in fleas

GEOGRAPHICAL DISTRIBUTION

Plague is present in many parts of the world and is probably most prevalent in parts of Africa and the East Indies No continent is free excepting possibly Australia The disease exists not only in cities as a rat epizootic but also in the less readily recognized form of sylvatic plague among rural rodents that are known to infest large areas in the United States South America South Africa and Asia Some of these infected areas are probably foci from which plague will spread again to the rat populations in cities when conditions become favorable

All the important foreign possessions of the United States except Alaska have had plague at some time during the most recent pandemic

The area of sylvatic plague infection in the United States at present extends over a great part of the western half of the country and over part of western Canada Squirrels prairie dogs field rats and some other rodents have been found harboring the disease

COMPLICATIONS

Pneumonia caused by the plague bacillus is occasionally seen as a complication of bubonic cases and this is thought to be sometimes the starting point of an outbreak of the pneumonic type of the disease

Prolonged suppuration of necrotic lymph nodes and indeed of other tissues may occur and occasionally lead to a fatal termination as late as a month rarely longer from the onset

DIAGNOSIS

In neither type of plague is there difficulty in clinical diagnosis in the presence of an epidemic Few diseases are more readily recognized by an experienced clinician once he is aware of the possibility of the presence of plague The situation is very different with the first cases in a community In these the diagnosis is necessarily dependent on laboratory confirmation which will be discussed later

DIFFERENTIAL DIAGNOSIS

The bubonic type with groin buboes may be mistaken for venereal infection with lymphatic involvement While the final diagnosis must rest on laboratory studies a few clinical points are of value The plague buboes are likely to be more rapid in development and more painful than are those of venereal origin the primary plague bubo most frequently develops in the region of the femoral lymph nodes whereas that due to gonorrhea or chancroid is usually in the region of the nodes along Poupart s ligament A final point of difference is that the plague bubo usually tends to be an elevation with a gradual slope a rounded low mound whereas the venereal swelling usually is sharper in its contour and more prominently elevated The presence of the venereal ulcer or a discharge may be helpful The constitutional symptoms always are more pronounced in plague

Tularemia which in certain animals bears close resemblance to plague is not likely to be a diagnostic problem in man The epidemiologic circumstances should be helpful in case of confusion the history of contact with wild rabbits or other rodents the bite of a fly or the bite of a tick would point to tularemia whereas the existence of plague in a community would suggest the latter diagnosis

The pneumonic form of plague may readily be mistaken for ordinary pneumonia or for pneumonia following influenza The nature of the prevailing epidemic and the certainly and rapidly fatal outcome of the plague pneumonia will aid in reaching a decision Final diagnosis in all important cases would depend upon the results of laboratory studies

BACTERIOLOGIC DIAGNOSIS

P pestis is one of the most readily identified of pathogenic bacteria regardless of its source In the lesions of both man and animals it usually occurs in

SYMPTOMATOLOGY

The incubation period of bubonic plague may be set at from three to twelve days but in most cases it will be four or five days

In the *bubonic* type the onset is usually sudden with fever often preceded by a chill or chilly sensations There are weakness and discomfort sometimes with headache and backache These are the usual indications of onset of several acute infectious diseases and except in the presence of a known epidemic of plague they are not likely to give a clue to the condition present The first specific indication that a given case is one of bubonic plague is likely to be pain and tenderness in the region of a lymph node or in a group of these usually about forty eight hours after onset of the general symptoms this is followed by swelling of the area and increase of pain and tenderness Often the bubo is present when the patient first is seen by the physician Leukocytes are said to be increased sometimes very markedly and blood cultures are likely to be positive even in many cases that recover The plague bacteremia may be very intense in cases that go on to a fatal issue

The location of the primary bubo appears to differ somewhat in different outbreaks It may be said however that half or more of the buboes will be in the groin with a larger proportion in the femoral than in the inguinal region perhaps one fourth will be in the axilla and a still smaller proportion in the cervical area and in some cases several regions will be affected There are always fever and marked prostration with mental confusion sluggishness and often delirium In patients who recover the fever usually begins to decline from the fifth to the tenth day and may reach normal a few days later In fatal cases the temperature usually remains high to the end Cases may terminate favorably by resolution of the bubo or by suppuration and subsidence of the general symptoms

The *septicemic* type presents general symptoms similar to those of the bubonic type but they are usually more severe These cases ordinarily are fatal within three or four days It is said that organisms may be so numerous in the blood as to be seen in blood films Some observers believe that there is usually a primary bubo in these cases but not in an area in which it may readily be detected

In the *pneumonic* type the incubation period is two or three days and the onset resembles that of severe pneumonia there are chills fever prostration pain in the chest cough and dyspnea and bloody sputum but with nothing characteristic It is to be noted that the sputum is blood stained or bloody but not rusty as in lobar pneumonia In all these cases there is plague septicemia and practically all patients die usually on the third or fourth day after onset *P pestis* is usually abundant in sputum smears but the laboratory diagnosis of pneumonic plague must not rest on smears alone Inoculation of animals is necessary to establish the diagnosis although obviously this step will be required only in special circumstances The presence of an epidemic and the speedily fatal termination of a group of cases usually make the diagnosis plain

Mice are highly susceptible but do not show sufficiently characteristic lesions to be of much service

Dogs and most other domestic animals as well as all birds are not susceptible to infection but cats appear to be moderately so and are thought to have been the source of a few human cases

The only organism bearing a close resemblance to the plague bacillus is Pfeiffer s bacillus of pseudotuberculosis of rodents (*Pasteurella pseudotuberculosis rodentium*) but this organism does not produce a sticky growth on agar and changes litmus milk to a deep blue which is permanent So similar is this organism to the plague bacillus that there is a degree of cross immunity between them Indeed this organism has been used as a prophylactic against plague in man but without much success Fortunately the pseudotuberculosis organism is very rarely pathogenic for man and does not produce in man pathologic changes resembling those caused by *P pestis* The organism causing tularemia does not resemble the plague organism although it does produce closely similar almost identical lesions in guinea pigs and squirrels

The plague bacillus as well as the tularemia organism has the important property of passing through the shaven skin of laboratory animals This property is of great value in isolating pure cultures of the plague organism from contaminated tissue of man or rodents

Serologic tests are not of great importance in the recognition of the plague bacillus The organism is difficult to bring into suitable suspension so that it can serve as an antigen for agglutination tests Complement fixation tests have been used but are of no special value except possibly to confirm a retrospective diagnosis When it is of great importance to establish beyond doubt the fact that a given infection in a human being or in a rodent is due to plague a serum protection test may be employed This procedure would be required only if the diagnosis were likely to be disputed or if it became necessary to establish the existence of plague infection in a new host in nature or in some other very special circumstance The protection test is carried out by giving each one of a group of laboratory animals preferably white rats an adequate dose of antiplague serum of proved potency This is followed by inoculation of these and an equal number of control animals of the same weight and from the same stock with the organism the identity of which it is desired to establish If the animals receiving antiplague serum survive while those not protected succumb to plague the question is answered in the affirmative If one wishes to eliminate the possibility of non specific serum protection a third group of animals may be given normal horse serum preliminary to the inoculation with the suspected culture These also should die of plague in a positive test

Immunity

It is customary to say that an attack of plague protects the individual against a subsequent infection Probably this is true but satisfactory data are wanting Active immunity is not readily produced in laboratory animals by the injection

pure culture and in large numbers as a short plump bacillus When suitably stained with carbol thionin or diluted carbol fuchsin it is seen to be bipolar It is gram negative In some specimens especially those taken from old lesions, some of the organisms are rather faintly stained coccoid forms more characteristic to an experienced observer than the so-called bipolar forms The questions as to whether the plague organism is motile or whether it has a capsule have been subjects of much difference of opinion It is a little difficult to see the importance of either point because other characteristics of the organism are so well marked

The significant cultural characteristics of the organism are well defined The plague bacillus multiplies at a lower temperature than many other pathogenic organisms While it grows well at 37° C it also multiplies satisfactorily as much as 10 C below this In primary isolation on ordinary nutrient agar the growth is shiny translucent and has the remarkable property of being very sticky so that when touched with a platinum needle or loop it may be drawn out in a long filament Old cultures long on artificial media often do not show this characteristic When grown on an agar base containing 2 5 or 3 0 per cent sodium chloride instead of the usual 0 5 per cent concentration the organisms have the remarkable faculty of being converted in forty eight or seventy two hours into very bizarre shapes such as globules of various sizes some enormous sausage like dumbbell forms and others resembling trypanosomes In broth the growth is in the form of a surface film with powder like masses adhering to the sides and the bottom of the culture tube If the tube is kept without vibration the culture remains clear and the so called stalactites may depend from the surface film but if agitated even slightly the culture may become turbid The morphology of the organism in broth culture usually resembles cocci in chains and careful observation may be necessary to show that the chains are made of short bacillary bodies The fermentation reactions in carbohydrate media are not important and apparently are not uniform for different strains On litmus milk the reaction becomes slightly acid in twenty four or forty eight hours and either remains so or returns to the normal blue The plague organism resembles other non spore bearing bacteria in its susceptibility to disinfectants drying and sunlight

As with other bacteria variants have been found among plague bacilli that designated by S being regarded as virulent and that designated by R as non virulent

The pathogenicity for laboratory animals of the virulent plague organism is very pronounced guinea pigs white rats white mice and rabbits all are susceptible rabbits less so than the others mentioned For most purposes the guinea pig is the animal of choice because it is highly and regularly susceptible with a fatal issue in from four to six days In this animal the lesions are uniform and rather characteristic hemorrhagic buboes multiple small necroses in the spleen and often a granular liver White rats are less uniformly susceptible but with the same inoculum usually die a little earlier than guinea pigs The lesions are less characteristic in artificially inoculated rats than in guinea pigs

used to inoculate the laboratory animals When such a pool is used the shaven skin technique is to be preferred and this method always is to be preferred for human or rodent material contaminated with other microorganisms Another procedure is in use in connection with the detection of rodent plague especially of squirrel plague Fleas are collected from rodents or from their nests ground in saline solution and used to inoculate laboratory animals This procedure has resulted in the finding of foci of infection that had not been detected by the usual examination of rodents

A number of infections usually fatal have occurred among laboratory workers engaged in plague studies which serve as a warning that the utmost care is necessary when handling plague infected tissues and animals or plague cultures

PROGNOSIS

The pneumonic type is almost invariably fatal Reported recoveries usually are regarded as evidence of erroneous diagnosis Death ordinarily occurs early on the second to fourth day The septicemic type also is highly fatal the death rate being over 90 per cent The death rate of the bubonic type differs in different epidemics from a minimum of about 15 per cent to a maximum of about 90 per cent In the various outbreaks in the United States the mortality has varied from about 30 to 90 per cent Death usually occurs at about the end of one week though some cases may have a fatal issue at a much later date

TREATMENT

Symptomatic treatment rest in bed good nursing and general supportive measures are to be employed as with other acute infectious diseases Suppurating buboes may be evacuated surgically

There is much difference of opinion with respect to the curative value of *specific serum* Antiplague serum of high protective power in laboratory animals does not necessarily give correspondingly favorable results in man In view of the lack of any definitely useful treatment unless some of the recently discovered chemotherapeutic agents may prove of value it is customary to use antiplague serum which should be given early in large doses intravenously Probably the serum is of no value in treating pneumonic plague

A number of chemotherapeutic agents have been used in the treatment of plague Iodine and mercury employed many years ago were found ineffective There is experimental and clinical evidence that sulfapyridine is of value and that sulfathiazole may give even better results but neither of these preparations has been used long enough or on a sufficiently large scale to warrant final appraisal

PROPHYLAXIS

The occurrence of plague in a community is likely to lead to alarm and disruption of commerce possibly out of proportion to the morbidity and mortality caused by the disease

Epidemic outbreaks of plague are most likely to follow water borne com

of killed cultures or extracts but living avirulent organisms give a high degree of resistance Immunity experiments are best carried on in white rats or white mice the extreme susceptibility of the guinea pig rendering it less suitable in this type of work Horses may be immunized against plague cultures with the production of an antiserum of good protective power in laboratory animals

Laboratory Diagnostic Technique

The securing and handling of materials for laboratory diagnosis are important When a bubo has developed in a patient so as to be readily recognized, it may be aspirated A small volume of sterile isotonic saline solution in a sterile syringe is injected into the gland withdrawn and nutrient agar slants and broth inoculated These may be incubated for twenty four hours or more and if the attempt has succeeded a pure culture is obtained which may be studied in detail Some of the withdrawn material may be used to inoculate guinea pigs The latter probably is the preferred procedure unless one has had previous experience with the direct culture method Smears from the aspirated material may show characteristic organisms

The morphology of the plague organisms derived from animal tissues is very suggestive almost pathognomonic but should never be relied on in making an important decision The great number of organisms usually present the fat bacillary bodies with deeply stained rounded ends the gram negative nature and the presence of coccoid forms are all of great significance in smears from fresh tissue and will often enable one to make a tentative diagnosis Blood cultures from the patient also may be successful but usually not so early as bubo cultures Autopsy material if fresh may be cultured in the way ordinarily used for other micro organisms but dependence should not be placed on this alone One should always inoculate laboratory animals (guinea pigs and white rats) with autopsy material since this is not only a surer way of securing a pure culture but has the added advantage of furnishing promptly the important evidence afforded by the gross pathology in the animals

When the material is from rodents the procedure is somewhat different In rats that have died from naturally acquired plague the gross pathology is so characteristic that unless it is especially important bacteriologic confirmation is not necessary In other rodents the gross pathology is not characteristic enough or is not sufficiently well known to be made the basis of a certain decision In any event it is better to resort at once to the inoculation of laboratory animals although pure cultures may often be obtained directly from naturally infected rodents The usual method is to place a small fragment of suspected tissue in a subcutaneous pocket in the groin or on the abdomen A little less certain but probably on the whole a more useful procedure is to rub suspected material into the freshly shaven skin of a guinea pig If the number of suspected animals is too great to permit the use of one or two laboratory animals for each suspected wild rodent tissue from ten or even more rodents from the same general locality may be mixed and

In attempting the control of rodents scientists have made efforts to produce epizootics that would exterminate them or at least greatly reduce the number When we consider that plague itself does no more than moderately and temporarily reduce the rodent population we cannot expect too much of artificially induced infections Members of the *Salmonella* group usually are used but in practical application they have not given encouraging results The mongoose has been employed for rat control but evidence of its effectiveness is by no means clear

Some success in the reduction of the rodent population seems to have attended the elevation of buildings so that cats and dogs natural enemies of rodents may have access to locations where rats often find harborage This of course is applicable only to temporary or light wooden buildings Permanent rat proofing by the installation of concrete or brick area walls and other construction that is unfavorable to rat harborage are much more effective measures

Special ordinances for the control of plague are required and in order to be effective must authorize the enforcement of measures designed to secure (*a*) rat proofing of buildings and docks (*b*) sanitary collecting and disposal of garbage (*c*) keeping of stables and domestic animals under sanitary conditions and (*d*) other provisions that may be necessary to meet special conditions for example the control of the squirrel population in rural or suburban parts of a city Under certain circumstances it may be important to require inspection of the dead during an epidemic to verify reported causes of deaths

In general urban plague suppressive measures may be regarded as very effective If the experience of the United States is a guide an outbreak of great extent is not likely to occur in a civilized community

The problem of human cases of plague due to the infection of wild rodents in rural areas is to be regarded as practically beyond successful control The regions involved are so large that the reduction of rodent population by intensive agriculture and the natural evolution of the epizootic are about the only factors that may be expected to reduce the hazards Obviously hunting of squirrels for food or diversion in infected regions is to be discouraged When an area of rural plague is adjacent to an urban community an attempt may be made to establish rodent free zones around cities to reduce the danger of infection spreading from wild rodent foci to rats in the cities The decision as to measures to be taken for the control of sylvatic (rural) plague will depend on the use to be made of the infected area and the extent of human population

The pneumonic type of plague is regarded as non communicable for the first twenty four hours and possibly for a slightly longer period In general serious risk begins when the patient begins to cough and expectorate and if transmission of the disease is to be prevented isolation must be started very early Early hospitalization of patients and early isolation of contacts should

merce This is well illustrated in the United States where they have occurred only at ocean and Gulf of Mexico ports

Maritime quarantine was first employed during the great pandemic of plague of the fourteenth century and continues to be one of the important control measures No longer however is it enforced by holding vessels outside of port for the traditional forty days but rather by attempts to destroy the rat population on ships usually by fumigation with toxic gas a mixture of carbon monoxide and carbon dioxide or sulphur dioxide or hydrogen cyanide The last named is the most frequently used and is a very effective deratting agent but it is highly hazardous for the personnel of a vessel and for the men doing the fumigation Many human fatalities have been caused by this and other fumigants consequently they should be used only by and under the direction of skilled disciplined and trained personnel

Maritime quarantine restrictions are important for vessels plying between *plague infected and non infected ports Ships should be fended* off from wharves hawsers should have metallic rat guards and rodent suppressive measures should be undertaken on vessels and on wharves Within comparatively recent years cargo and passenger vessels have been constructed in a manner that leaves little encouragement for the harborage of rats and it is not too much to hope that sea borne carriage of plague which has *led to* world wide outbreaks will in the not distant future be a matter of historical interest only

Public health measures on land may be divided into those applicable to urban outbreaks due to rat infection and those due to plague among rodents in rural areas

In urban communities the procedures may be described broadly as those necessary to diminish and control the rat population The measures are usually undertaken by an organization established in a health department and directed exclusively to plague control A headquarters is set up the area if large enough is divided into districts for administrative purposes and a laboratory for diagnosis of human and rodent plague is established Antirat measures consist of poisoning trapping and destruction of rat harborage These measures are designed to meet emergencies Among the various poisons commonly employed are barium carbonate arsenic and red squill the last named has the advantage of being relatively non toxic to human beings

For long continued protection of the community the measures mentioned must be carried out and in addition extensive structural changes of docks warehouses and other business buildings are often necessary Usually these improvements are desirable quite apart from the menace of plague The places most likely to harbor rats in large numbers are food depots stables warehouses markets and slaughterhouses Since the discovery of the importance of rodents in the transmission of diseases other than plague especially endemic typhus and Weil s disease and in view of the destructiveness of rats measures looking to their control should meet but little opposition

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prove effective but the difficulties in carrying out both of these procedures limit their probable usefulness

Personal prophylaxis may be practiced by avoiding infected areas or when this is impossible or impracticable one may use biologic preparations These fall under two heads (1) Antiplague serum may be used with hope of success in such a special circumstance as a wound received at an autopsy on a plague cadaver—human or animal—or other especially hazardous exposure (2) Antiplague vaccine may be used for the general population The decision as to whether this will be employed will necessarily depend on the probable extent of the disease in man in other words it will depend on the hazards to which the population is likely to be subjected For example on the basis of experience of the most recent pandemic no outbreak of plague in North America or Europe is likely to be of such magnitude as to warrant general use of any vaccine now available With an outbreak of plague in prospect such as occurred in India and elsewhere in the Orient in the last years of the nineteenth and early years of the present century or such as has existed in parts of Africa and in parts of the East Indies in recent years one probably is justified in advocating general vaccination though there is no convincing evidence that an outbreak has been suppressed by this method The number of vaccines that have been employed is good evidence that none is completely satisfactory Only two will be mentioned (a) The vaccine originally introduced by Haffkine is composed of killed pest bacilli It has been very extensively used in India with results usually regarded as favorable but the early reports of high effectiveness have not always been confirmed (b) The most recent prophylactic against plague is that devised by Otten working in the Netherlands East Indies It is a living vaccine made from a strain of *P pestis* selected for its high antigenic efficiency as shown by experiments on animals and man In large scale tests in Java there appeared to be a very great reduction in the plague mortality It may be said that the living vaccine of Otten seems to offer a better prospect of success than any other biologic prophylactic There is no satisfactory evidence that any preparation is of value in dealing with pneumonic plague

There is little or no danger of direct transmission of the purely bubonic type of plague from person to person but when such a patient develops a secondary pneumonia there is risk of transmission Physicians nurses and others caring for the primary pneumonic type of plague are subject to great hazards and the utmost in the way of precautions is necessary to guard against infections of personnel Goggles masks (eight layers of gauze) rubber gloves for the attendants and strict isolation of the patients are useful precautions

Obviously antiplague measures must be modified to meet special local situations Thus it may be advisable to move the whole population from a badly rat infested village while other effective measures are being taken Local opposition to public health measures may make it necessary to do far less than is desirable Education of the public to the need for antiplague measures is an essential part of every antiplague campaign

filamentous forms the so called involution forms It is killed rapidly by all the usual germicides and by heat at 65 C in ten minutes

EPIDEMIOLOGY

The disease occurs in nature as a highly fatal septicemic infection of rodents gallinaceous birds and a few other animals such as the opossum fox and coyote In this country rabbits and hares constitute the most important animal reservoir The infection is transmitted and perpetuated by a number of ectoparasites such as ticks lice fleas and flies of which the most important are the rabbit tick *Haemaphysalis leporis palustris* and the western and eastern wood or dog ticks *Dermacentor andersoni* and *Dermacentor variabilis* Since these ticks transmit the infection through their eggs to succeeding generations these arthropods constitute another reservoir of natural infection (Philip)

Although human infections have resulted from direct contact with the tissues or pelts of the fox squirrel gray squirrel flying squirrel muskrat woodchuck vole opossum coyote fox quail prairie chicken pheasant and sheep as well as from the bites or scratches of the skunk coyote squirrel Montana ground squirrel rat cat dog hog opossum sheep bull snake and snapping turtle the principal sources of human infection are the jack rabbit cottontail rabbit and snowshoe hare At least 90 per cent of human infections in America Europe and Japan have followed contact with infected tissues body fluids or pelts of rabbits or hares Infection by ingestion is not rare Several small outbreaks have occurred as a result of eating insufficiently cooked rabbit meat The vole appears to be the principal source of infection in Russia In our western States many human infections have been transmitted by the bite of the horse fly or deer fly (*Chrysops discalis*) In any part of this country infection may be transmitted by tick bites by *Dermacentor andersoni* or *Dermacentor occidentalis* in the West and by *Dermacentor variabilis* elsewhere Bedbugs mosquitoes stable flies and house flies have transmitted infection under experimental conditions but are not known to have caused human disease It is important to bear in mind the well demonstrated ability of *Bact tularense* to penetrate normal unbroken skin and mucous membranes Water borne outbreaks of considerable size have occurred in Russia *Bact tularense* has been recovered from the water of streams in Montana in association with an epizootic among beaver

Geographical Distribution The present geographical distribution of the disease is the United States Alaska Canada Japan Russia Norway Sweden European and Asiatic Turkey Czechoslovakia and Austria

PATHOLOGY

The most frequent sites of gross tularemic lesions are the skin lymph nodes spleen liver and lungs Primary lesions originate as small inflamed papules which enlarge ulcerate liberate necrotic cores and become indolent painful ulcers with a punched-out appearance elevated margins and ragged necrotic

CHAPTER XIV

TULAREMIA

LEE FOSHAY

TULAREMIA IS A NATURAL DISEASE OF WILD RODENTS AND their ectoparasites caused by *Bacterium tularense* It is readily transmissible to man producing a bacteremic disease with variable clinical manifestations It is characterized by abrupt onset with chills and fever severe generalized aches and pains development of painful buboes prolonged morbidity and low mortality In many of its features the disease exhibits a striking resemblance to plague The incubation period varies from less than twenty four hours to thirteen days but is usually from two to five days

HISTORICAL NOTE

During investigations on rodent plague in 1911 McCoy discovered tularemia as a natural infection of California ground squirrels In 1912 he and Chapin isolated the causative agent and named it *Bacterium tularense* from Tulare the county in which the disease was first observed Infection of man was demonstrated in 1914 by Wherry and Lamb who also discovered the natural reservoir of infection in wild rabbits Francis in 1919 identified the Pahvant Valley plague or deer fly fever as tularemia in the initial report of a long series of brilliant investigations which forms the basis of our present knowledge of the disease Francis gave it the name tularemia It is doubtful if the incidence of the disease is increasing The apparent increase is probably due to increase in its recognition Prior to 19 4 only 15 cases had been reported From 19 4 to 1935 the number of reported cases in the United States was 6 206 In recent years the reported cases in this county have averaged about 000 annually

ETIOLOGY

Bact tularense is a small gram negative non sporulating highly pleomorphic micro organism usually showing coccoid and bacillary forms occasionally bipolar forms It has no flagella and true motility is never observed It is an obligate aerobe and will not grow in the absence of cystine or cysteine It is like *Pasteurella pestis* in that capsules occur in both virulent and avirulent strains also in its production of large spherical hourglass flask shaped and

about normal for from one to three days and a secondary rise to the initial height which lasts for about two weeks followed by a gradual decline to normal Cough is a frequent early symptom commonly transitory seldom persisting for more than two weeks

A non pathognomonic exanthem occurs in 20 per cent of cases Although variable in type it is usually papulovesicular and occurs most frequently on the back of the neck shoulders face and arms (Hitch and Smith)

Hematogenous bronchopneumonia occurs in about 18 per cent of cases It is better considered as an integral part of the disease than as a complication (Blackford and Casey) Although pneumonic areas may arise in any lobe they are commonly hilar at the onset producing neither symptoms nor physical signs Extension and confluence may result in a lobar distribution Pleurisy dry or with effusion may occur

The acute febrile phase of the disease usually lasts from three to four weeks Profound weakness anorexia loss of weight recurring chills sweats and severe prostration are noted Pneumonia and its complications are the chief causes of prolongation of the acute phase

Suppurative lymphadenitis occurs in slightly more than half of all cases which develop *buboes and most frequently during the second month of disease* The duration of disease varies greatly from two weeks to fourteen months The average duration is almost four months Delayed suppuration of a series of buboes is a frequent cause of protracted illness also the progressive or migratory pneumonic lesions and their sequelae and the persistence of infection in large serous cavities Convalescence is slow Return to work at the end of a month is rare Commonly the patient spends the second month at home partially ambulatory due to weakness on exertion In many cases half time work can be performed during the third month

Relapses occur infrequently appearing from eight months to two years after onset They are usually of brief duration A second relapse occurs very seldom Residual symptoms or disability are uncommon True chronic tularemic infection is a clinical rarity although it is a very disabling condition usually characterized by intermittent attacks of fever malaise great weakness re enlargement of previously involved lymph nodes sweats and mental depression With the exception of these rare cases recovery from attack confers permanent immunity Subclinical or inapparent tularemic infection has not been demonstrated

The clinical types of the disease are

Ulceroglandular with dermal primary lesion and regional buboes This is the most common type and it accounts for 87 per cent of all cases

Oculoglandular with conjunctival primary lesions and regional buboes occasionally confused with Parinaud s conjunctivitis The type frequency is 2 per cent

Glandular with buboes but without primary lesions The type frequency is 5 per cent

floors Lymph nodes show enlargement acute congestion edema and areas of focal caseation or liquefaction necrosis The spleen is enlarged dark red soft and friable Its surface and cut sections usually show few to many gray white foci of necrosis submiliary miliary to 0 5 cm in size The liver is enlarged with foci of necrosis similar to those in the spleen The lungs may be normal or may show the following lesions separately or in combination miliary foci of necrosis few or solitary discrete nodules with caseation necrosis or lobular pneumonia which may be confluent

Microscopic lesions are granulomatous in type characterized by subacute ness approaching chronicity The chief cellular reaction is reticulo-endothelial-epithelioid-monocytic Pneumonic sections may show principally macrophages Early lesions show simple necrosis and extensive karyorrhexis Advanced lesions are tuberculoid with central caseation necrosis concentric zones of epithelioid cells radially arranged fibroblasts lymphocytes and occasional peripheral giant cells Collected necropsy reports show that microscopic lesions may occur in almost every tissue or organ The wide distribution of lesions is referable to (*a*) an initial bacteremia which usually lasts from five to ten days (*b*) per sisting bacteremia or (*c*) terminal septicemia which usually occurs five to seven days ante mortem and which appears to be the chief cause of death Bacteria are very seldom observed in the lesions The pathologic changes in rodents closely resemble those of plague

An excellent monograph on the pathology of tularemia was published by Lillie Francis *et al* in 1937

SYMPTOMATOLOGY

Although four clinical types were originally described by Francis their gen eral symptoms are identical The onset is characteristically sudden and severe with aching bodily pains chilliness chills fever (averaging 104 F) profuse sweats headache nausea and vomiting Primary lesions usually appear before buboes but occasionally this order is reversed *Either* or *both* are usually mani fested within forty-eight hours after the initial chill The location of the initial papules varies depending on the mode of transmission but most of them appear on the hands or face Infrequently they occur within the oral and pharyngeal cavities They are absent in 10 per cent of human cases Unless *there is secondary infection of the primary lesion* a characteristic feature of tularemia is complete absence of visible lymphangitis between the primary lesion and regional buboes Regional lymph nodes are involved first with painful tender progressive enlargement Remotely situated nodes may en large later Unilateral ulcer with bilateral buboes is not a rare finding Dermal lymphangitic nodules appear infrequently (7 per cent incidence) along the courses of lymphatics usually on the forearms They resemble closely the le sions of sporotrichosis

Fever is always present characteristically daily remittent in type Very fre quently there is an initial rise lasting from three to five days a remission to

agglutinate the *Brucella* and vice versa. Usually the higher titer indicates the disease that is present (Francis and Evans). An informative study on agglutination was reported by Ransmeier and Ewing.

Diagnosis may also be confirmed by cutaneous reactions produced by intradermal injection of very light suspensions of killed *Bact. tularense*. Positive reactions have the appearance of positive tuberculin tests. The reaction is read forty-eight hours after injection is made. The test suffers from the faults common to all skin tests, but it is as reliable as any. The chief advantage is that the great majority of tests become positive during the first week or ten days of disease when the agglutination test is almost invariably negative. During the first week of disease about 7 per cent of patients show negative initial tests. Retesting at forty-eight hour intervals greatly diminishes the proportion of diagnostic failures prior to the appearance of serum agglutinins. Later in the disease the reliability of the test approaches that of the agglutination test. The test is best used to supplement, not to supplant, the agglutination test. Skin reactivity, like serum agglutinins, may persist for many years. The writer has seen positive reactions as late as twenty-two years after recovery.

Bacteriologic diagnosis is occasionally possible by direct inoculation onto solid media of blood drawn during the stages of initial bacteremia or of septicemia, by similar cultivation of exudates from primary lesions or from serous cavities. Far more reliable is the inoculation of infected body fluids, including sputum, into guinea pigs or other rodents and the cultivation of the organism from the heart blood at rodent autopsy. For multiplication the organism has an obligate requirement of cystine or cysteine, and it grows poorly, if at all, in simple liquid media. Blood-cystine agar is the medium of choice, and added glycerine is superior to dextrose. It is useless to examine stained smears of exudates from primary lesions or suppurated nodes. Manipulation of infected animals entails great risk of infection. This work should be done by recovered immune or well-vaccinated persons. Many laboratory infections have occurred.

There are no characteristic alterations in the blood. Mild to moderate secondary anemia may occur during the first month. Leukocyte counts range from 5,000 to 10,000 with polynucleosis, but are useless as diagnostic criteria.

Diseases commonly mistaken for tularemia are influenza, pneumonias of other etiology, Parinaud's conjunctivitis, and sporotrichosis. In regions where both infections are endemic, plague should be considered.

PROGNOSIS

Although man is very susceptible, he usually develops a high degree of natural resistance after infection occurs, and the prognosis in regard to survival of untreated cases is good. The case fatality rate is about 6 per cent. Rare individuals develop little or no resistance, and the overwhelming septicemic disease runs a rapidly fatal course in from five to ten days. Most deaths occur during the third week. The prognosis is less favorable if pneumonia is present, especially if consolidations are large and expanding, and it becomes worse if delirium and confusion appear. The advent of septicemia makes the prognosis

Typhoidal characterized by absence of both primary lesion and buboes It accounts for 8 per cent of cases The frequency of pneumonia is three times and the type fatality rate is four times that of the bubonic types

COMPLICATIONS AND SEQUELAE

The most serious complication is septicemia It is invariably fatal in untreated cases Infrequently it occurs during the first week accounting for most deaths prior to the twelfth day of disease The period of greatest danger is from the thirteenth to the twentieth days of disease The supervention of septicemia may be gradual more commonly it is fairly abrupt and is betrayed by the following diagnostic triad (1) sustained high fever succeeding the previous daily remissions (2) *intensification of delirium and confusion to* a stuporous or semicomatose state and (3) rapid enlargement of the liver and spleen

Bronchopulmonary lesions may result in bronchiectasis extensive pleuropulmonary fibrosis empyema and lung abscess Peritonitis and pericarditis occur infrequently Meningitis encephalitis enteritis and thrombophlebitis are less common

From one to three years after apparently complete recovery large buboes may again develop at previously involved sites More than half of them suppurate

DIAGNOSIS

The clinical diagnosis is usually easy except in cases of the typhoidal type A history of recent contact with wild rodents of tick bite or fly bite with abrupt severe onset early appearance of persisting primary lesions and buboes and continuing remittent fever usually indicates tularemia and rarely fails of diagnostic verification by standard laboratory procedures of amazing reliability More frequent early recognition of cases of the typhoidal type in which pneumonia often dominates the picture has been the experience wherever physicians have remembered to consider the disease its regional modes of transmission and seasonal incidence

Laboratory diagnostic procedures have a reliability which approaches perfection The standard test is agglutination So far as is known agglutinins have never failed to appear in the serum of any surviving patient In fatal cases the test is usually positive unless death occurs before the end of the second week The test never becomes positive before the eighth day of disease Agglutinins appear usually during the second week seldom are delayed into the third week and rarely into the fourth week The usual titers are first week 0 second week 1 40 to 1 80 third week 1 3 0 to 1 640 fourth week 1 640 to 1 560 A titer of 1 °0 is suspicious one of 1 80 is diagnostic if *Brucella* are not also agglutinated Successive tests showing ascending titers to a high level in the third week are completely convincing Once agglutinins have appeared as a result of infection they persist in slowly diminishing titer for many years probably for the life of the individual Rare examples of disappearance have been *noted Serums from tularemia patients* occasionally cross

tions and dosage The serum treatment of tularemia is analogous to that of plague in many respects The writer cannot summarize his eleven years of experience with tularemia in better words than those written by Wu Lien Teh on the serum treatment of plague We have learnt that the serum though far from being ideal is likely to save many lives if (*a*) its administration is started at the earliest moment (*b*) it is applied in sufficient amounts intravenously and (*c*) repeated doses are given conformable to individual requirements Serum therapy effectively terminated continuing disease up to the ninth or tenth months Thereafter it has proved ineffective There is no satisfactory therapy for the chronic form of the disease Serum and vaccine therapy have been unsuccessful Early serum therapy apparently prevents it

Management of Special Symptoms Primary lesions should not be incised They are necrotic not suppurative and incision serves no useful purpose Wet dressings of saturated solution of magnesium sulphate or of freshly prepared half saturated solution of urea are useful Ocular lesions require continuous applications of warmed solutions of magnesium sulphate and sodium chloride with frequent lavage of the conjunctival sacs with warmed boric acid saline solution Germicidal collyria contribute no additional useful effects Hot packs hot soaks and radiant heat are more effective than drugs in relieving the pains in muscles joints and buboes

PROPHYLAXIS

Although lay technique of management of rubber gloves sometimes falls short of the ideal it is advisable for hunters and cooks to wear them when they handle wild rabbits Thorough cooking makes all edible game non infectious Laboratory workers should soak the fur of animals with dilute mercuric chloride solution before performing autopsies There is no wholly satisfactory method of preventing infection from fly bite or tick bite The writer and his associates have recently published the results of a nine year study on vaccine prophylaxis in 100 exposed individuals There seems little doubt that to a considerable extent the disease can be prevented or greatly modified by vaccination

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extremely bad Death usually follows within seven days There is no record of recovery of an untreated patient with septicemia and very few with high colony counts by blood culture have survived even when serum administration has been prompt and copious The outlook is not good for patients who have coronary or rheumatic heart disease or for patients over fifty years of age The mortality risk of the typhoidal type is four times that of the bubonic types Most deaths are preceded by septicemia some by toxemia hyperpyrexia and circulatory failure Except for minor local reinfections second attacks have not occurred (Francis 1936)

TREATMENT

Rest in bed good nursing supportive diet and standard measures for symptomatic relief form the basis of treatment There is no need for rigid isolation or for unusual sick room precautions because man to man transmission is extremely rare

The nature and distribution of pathologic lesions and the normal course of the untreated disease have not always been considered in reports and discussions on therapy (Unwarranted expectations have been unfulfilled because the remedy used did not constantly produce unqualified results On the other hand claims of exceptional merit have been advanced for other remedies with supporting citations of measurable aspects of morbidity which fall squarely on the means or modes of comparable data derived from a large series of untreated cases) No single form of therapy has met with unqualified approval Mercurochrome metaphen neoarsphenamine quinine iodides acriflavine and other dyes have their proponents and opponents The same holds true for drugs of the sulfonamide group No controlled studies have been reported which show that any of these drugs has appreciably altered the course of disease Laboratory evidence of the usefulness of sulfonamides in experimental tularemia has not been demonstrated Carefully controlled unreported in vitro studies by an associate who used large medium and small inocula showed that *Bact tularense* is unaffected by any of the sulfa drugs except sulfapyrazine and sulfadiazine and by these to an extent not indicative of marked therapeutic action The writer has knowledge of about 90 patients who were given thorough treatment with sulfonamides with blood concentrations maintained at optimal levels the treatment instituted early and in the absence of detectable visceral lesions There was no evidence of significant modification of the disease even by sulfapyrazine or sulfadiazine Some patients in each of the groups that were receiving sulfanilamide sulfapyridine sulfathiazole and sulfadiazine developed pneumonic lesions which progressed in the usual manner In some there occurred pleurisies with effusions from which virulent *Bact tularense* was recovered Since 6 of these patients died there was no reduction in mortality

In a controlled study of 600 unselected cases Foshay demonstrated clinically and statistically that specific serum therapy significantly shortened morbidity and diminished mortality This report gives detailed information on indica

CHAPTER XLVI

UNDULANT FEVER (BRUCELLOSIS)*

A. V. HARDY

BRUCELLOSIS (UNDULANT FEVER, MEDITERRANEAN FEVER, gastric fever, Malta fever, rock fever, Gibraltar fever, melitococcic fever, goat fever, Texas fever, Rio Grande fever, Brucella fever, Bang's fever) in man is a systemic or focal infection caused by *Brucella melitensis*, *Brucella abortus* or *Brucella suis*. The disease is characterized by weakness, fever with morning remissions, occipital or frontal headache, muscular pains, profuse sweats, chills, constipation, secondary anemia, nervous disturbances and metastatic involvement of joints, the eyes and the reproductive organs. The course of the disease is of indefinite duration but may be marked by repeated relapses and may become chronic. The mortality is low.

HISTORICAL NOTE

The first full and accurate description of the disease was given by Marston in 1861, who called it Mediterranean or gastric intermittent fever. The disease in human beings caused by *B. melitensis* was named "undulant fever" by Hughes in 1897. (For a complete bibliography of the literature on the disease Huddleson (1939) should be consulted.) It is of interest to note that the first authentic case of brucellosis originating in the United States was reported by Craig in 1905. At the same time Mr. Thompson of the United States Bureau of Animal Industry brought 65 goats to the United States from Malta. Of 12 men in the crew of the S.S. *Joshua Nicholson*, 8 became ill with Malta fever while the others, who either drank little of the milk or boiled it, remained well. After the goats were placed in quarantine at Athenia, New Jersey, a woman also drank some of the milk and developed the same infection. All the goats were slaughtered. Dr. Alice Evans (1918), in an extensive series of researches, showed the relationship between *B. abortus* and *B. melitensis*. Since that time much work has been done on undulant fever.

* With the permission of the publishers the clinical observations presented here are drawn from the author's section in Huddleson's "Brucellosis in Man and Animals," The Commonwealth Fund, New York, 1939.

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PATHOLOGY

Although a considerable number of postmortem examinations on fatal cases of brucellosis have been recorded few gross changes with the exception of enlarged spleen and superficial lymph nodes were observed which could be attributed directly to invasion of *Brucella* In Iowa in one fatal case reticulo-endothelial hyperplasia of lymph glands and centrolobular necrosis and degeneration of the liver were observed In another the changes seen were chronic interstitial pancreatitis chronic cholecystitis fatty infiltration of the liver passive congestion of the liver and fragmentary myocardial degeneration The morbid anatomic changes in human brucellosis have been extensively reviewed by Sprunt and McBryde (1936) They have also described the following anatomic changes in one fatal case of their own of *Brucella* infection Extensive destruction of the blood with deposits of hemosiderin in the liver spleen and kidneys cloudy swelling of the hepatic cells and fatty changes in the liver necrosis of the convoluted tubules of the kidney fibrinous and proliferative pleuritis pleural effusion edema of the glottis laryngitis tracheitis tracheotomy wound terminal staphylococcic infection and acute mediastinitis Pagley Mueller and Wells (1936) reported a fatal case of brucellosis due to *B abortus* in which death was caused by a pulmonary embolism

SYMPTOMATOLOGY

Marston (1861) stated that there is no fever so irregular as this in its course and symptoms and Craig (1903) stated that it is extremely difficult to describe accurately all the forms which this truly protean disease may assume Brucellosis was first classified by Hughes (1897) on the basis of difference in temperature curves namely the malignant the undulant and the intermittent This author recognized also an ambulatory form and mentioned irregular mixed and chronic varieties These types have been observed in cases of infection with the more recently discovered varieties of *B melitensis* In Malta brucellosis is a disease of variable severity (Debono 1939) ranging from a mild and hardly recognizable form to a virulent and rapidly fatal infection The background of the infection is a highly irregular fever rising and falling remitting and recrudescing forming a series of waves but following no regular course and persisting for long periods the name simple continued fever by which the illness was formerly known adequately expresses the essence of the disease in the majority of cases The other cardinal symptoms are enlargement of the spleen a tendency to profuse perspiration and rheumatic manifestations toward the end of the infection The disease runs a subacute or chronic course lasting for weeks months or even years but is frequently broken by acute episodes and complications such as bronchitis bronchopneumonia hepatitis perisplenitis and orchitis The patient is gradually reduced to a state of profound anaemia and inanition reminiscent in some cases of advanced tuberculosis or malignant disease Eventually the fever burns itself out although it is a long time before the patient is able to return to his work

EPIDEMIOLOGY

No broad areas have been shown to be free from brucellosis infections in animals and man Variations in incidence are in part explained by differences in accuracy of diagnosis In Malta Debono (1939) has pointed out that the prevalence of brucellosis varies from year to year Cases of brucellosis occur all the year round in Malta but there is a marked increase during the months of July August and September He attributed this seasonal incidence to the fact that the principal kidding season is in March and April and that the more active excretion of *Brucella* takes place during the first months of lactation

In Malta brucellosis was formerly more prevalent in urban and suburban districts but lately the rural districts seem to have suffered more in proportion to their population Country people seem to drink less milk than town dwellers but the discrepancy is explained by the greater opportunity for direct contact with infected animals

Age and sex distribution of brucellosis indicates that in the United States young adult males are more heavily infected and that there is a relatively low incidence in females and in children Debono calls attention to the fact that in Malta there is little difference in incidence between sexes but that there is a much higher mortality in females The disease is most common in Malta among children under five years of age Although the frequency of brucellosis is high in Malta because milk forms the principal item of diet for rich and poor alike the mortality is very low and often a subclinical infection confers lasting immunity These unrecognized infections in childhood may explain the greater resistance of the Maltese as compared to the extraordinary susceptibility of English soldiers and sailors in the days before the source of infection was recognized

Occupational studies indicate a comparatively high rate for men working on the farm and the excessive ratio for packing house workers strongly emphasizes the risk in occupations involving direct contact with livestock and fresh meat As a result of the studies of the Mediterranean Fever Commission it was assumed that brucellosis was acquired through ingestion of raw infected dairy products but it has been established through experimental studies that infection may be acquired through cutaneous contact with infective secretions or tissues

ETIOLOGY

The causal agent in brucellosis is a micro organism with the generic name *Brucella* *B melitensis* *B abortus* and *B suis* have been recognized Special cultural methods are necessary for the isolation of these organisms The cultural differentiation and the serologic methods of differentiation of the genus *Brucella* are given in detail by Huddleson (1939) and may also be found in the standard textbooks of bacteriology To be of value these studies must be carried out by an expert bacteriologist

be weakness and anorexia or weakness alone The severity of these cases varies so that while some are confined to bed for only a few days others suffer from a prolonged infection which terminates fatally Most such infections last between six weeks and four months while about one third of this period is spent in bed Morning temperatures are between normal and 38 C (100 4 F) and evening temperatures from 38 5 to 40 C (101 3 to 104 F) The fever terminates by slow lysis

Ambulatory Type Twenty five per cent of the Iowa cases were of this type and Simpson (1930) reported that one fourth of his patients experienced a relatively short and mild illness and that about 1 per cent remained at work throughout

The onset in these cases is insidious weakness being the one constant symptom and occasionally the only one noticed All the symptoms described in the intermittent form were found in some of the mild cases Physical examination usually reveals no abnormality although in some patients the spleen is palpable The temperature is normal in the morning but may reach 38 5 C (101 3 F) in the evening The duration of the mild form of brucellosis varies from two weeks to several months but more often is more than one month and less than four months

Undulant Type The distinguishing features of these cases are the occurrence of relapses When intervening short periods of apyrexia occur the temperature records have a wavelike appearance This feature is more common in the Mediterranean cases but is met only occasionally in infections with the *abortus* or *suis* variety Of the Iowa cases and also of Simpson s Ohio cases 15 per cent suffered relapses but even in these the typical undulations were rarely observed Characteristically the temperature decreases by a gradual lysis Occasionally such a train of symptoms was repeated several times in the same patient In other cases the disease began as the usual intermittent type and was followed at variable intervals by one two or more relapses These usually decreased progressively in intensity and duration

Malignant Type Infections of this type with *B abortus* or *B suis* are rare They are characterized by sudden onset an acute course and usually by fatal termination In most cases the temperature is high and sustained with an extreme hyperpyrexia occurring before death There are great prostration severe headache and backaches marked anorexia and usually true rigors and constipation Sooner or later delirium and coma appear Perspiration is not profuse The spleen is likely to be much enlarged The duration of malignant brucellosis two cases of which were observed in Iowa was about three weeks

Atypical Chronic Type In the diagnosis of brucellosis due consideration must be given to the occurrence of atypical forms of the disease These infections may closely simulate other diseases and an accurate diagnosis is then dependent on laboratory findings The chronic form of the disease may at times present manifestations resembling the ambulatory form of typhoid fever tuberculosis bronchopneumonia meningitis cystitis rheumatism and various surgi

as convalescence is often accompanied by marked physical weakness and mental inertia (Debono 1939)

Onset The onset of brucellosis may be either sudden or insidious During this period the symptomatology is extremely varied In some cases an acute respiratory infection including sinusitis precedes the prolonged illness and in others cystitis or pyelitis apparently first give concern Whether the onset is rapid or insidious the infection is at first marked by symptoms that are characterized by their similarity although they may differ markedly in intensity Varying degrees of lassitude weakness lack of energy or tiring easily were the initial symptoms in more than 50 per cent of the patients studied in the Iowa series Headaches gave the first indication of illness in 10 per cent while in others chilliness anorexia and general aching were noticed

In the cases studied in Malta by Debono the onset was acute in 60 per cent although careful investigation revealed that for some time the patient had not felt well and had suffered from physical tiredness and mental lethargy According to this observer the usual symptoms are headache general malaise vague bodily pains pains behind the eyes and a raised temperature Such cases are often diagnosed as influenza in winter or sandfly fever in summer The diagnosis in the first few days is almost impossible He points out that the initial symptoms may be gastric with anorexia nausea vomiting pain in the epigastrium and symptoms suggesting indigestion enteric or paratyphoid fever and rarely appendicitis or cholecystitis Debono concludes that there is nothing characteristic about the onset of brucellosis and the disease is usually diagnosed as something else in the first few weeks It is only after this when the spleen becomes palpable and the temperature curve begins to assume a characteristic shape that the diagnosis is revised It is usual in Malta to test the blood for *Brucella* infection in every fever lasting for more than a few days no matter how suggestive of other disease the symptoms may be

Intermittent Type Most of the Iowa cases were of the intermittent type In most of these cases the onset is insidious a sense of progressing afternoon weariness first oppressing the patient General aching some headache distaste for food spells of chilliness in the early evening and moderate insomnia follow in turn and there is sometimes a suspicion of fever Backache stiffness or pain in the neck and joints constipation and loss of weight are added to the accumulating signs and symptoms A hacking cough which is sometimes present may be persistent Night sweats occur later in the course of the disease These are frequently drenching in character Sometimes repeated rigors take place It is usually a matter of weeks before these patients seek medical advice and in many instances the patients have great difficulty in defining their ailments or perhaps they complain chiefly of one of these symptoms Physical examination usually reveals no abnormalities except signs of anemia weakness and loss of weight although sometimes the spleen is palpable or the abdomen tender With mild infections they might get up in the morning but might be glad to rest in the afternoon The most persistent symptoms may

fused and cyanotic the tongue dry and brown the teeth covered with sordes the liver is usually enlarged vomiting is frequent and the urine which is scanty and loaded with albumin may be suppressed in the final stages The delirium is acute at first but soon gives place to apathy and bed picking The pulse which is over 120 per minute from the beginning becomes thready and intermittent typanitis develops and death takes place either from cardiac or renal failure in ten to twenty-one days All the symptoms point to severe septicemia The mortality is 40 per cent

Weakness is the one symptom that was certainly present in all cases although in mild infections it is often experienced only in the afternoon Occasionally it constitutes the only subjective manifestation of the disease During the period of onset it is the most common symptom during the fastigium in two-thirds of the cases it is the most prominent or severe and during convalescence the most persistent

Sweating is the most distinctive feature of the disease and occurs in 84 per cent of the cases It may be present from the onset and if so it should give rise to the suspicion of brucellosis at an early stage The symptom of sweating was also noted in the Malta series of cases reported by Debono who called attention to the fact that the sweats appear with the decline of each pyrexial wave and especially when the temperature is markedly intermittent In 53 per cent of the Iowa series of cases the sweating was profuse or moderately so It occurred soon after midnight and was of short duration

The sweating at times was quite prolonged necessitating several changes during a single night or it occurred irregularly whenever the patient slept even in the afternoon Debono calls attention to the fact that in Malta the sweating occurs in the earlier part of the night earlier than in pulmonary tuberculosis The sweats are one of the most unpleasant features of brucellosis

Chilliness was a symptom of the period of invasion in the Iowa series of cases and occurred in association with the daily rise of temperature It was experienced in 77 per cent of the cases and usually gave little discomfort

Other symptoms which have been observed in both the Iowa cases and those reported from Malta by Debono include pain which is not a serious symptom Usually the physician is impressed by the patient s almost complete freedom from pain Gastro-intestinal symptoms are rarely troublesome except in the moderately severe cases In Malta gastric disturbances are more frequent At the onset and during the climax of the pyrexial waves there may be marked anorexia Epigastric tenderness is common and persistent vomiting is a bad prognostic sign Constipation is the rule but diarrhea may occur in the more severe cases and may give rise to confusion with typhoid fever

Enlargement of the spleen is one of the cardinal signs of brucellosis The splenomegaly usually persists throughout the course of the infection but the spleen may exhibit alternations in size growing and diminishing with the waves of pyrexia Symptoms referable to other systems such as the respiratory cardiovascular urogenital and nervous systems have been observed in both the Iowa and Malta series of cases

cal conditions No symptoms or signs may appear in chronic cases which even suggest a diagnosis of brucellosis There may be no history of an acute attack accompanied by a high elevation of temperature chills and sweats Both cultural and serologic examinations may remain negative throughout the course of the illness The only complaints occurring the first months of the disease may be exhaustion and occipital headaches Pains in the joints and back are common Many patients speak of vague gastric disturbances and pain in the right lower quadrant the latter sufficiently marked to suggest chronic appendicitis According to Huddleson the temperature in these cases is slightly elevated in the evening but may be subnormal in the morning and normal in the afternoon and even weeks may pass without notable fever Some patients gradually manifest neurologic symptoms such as mental depression apprehensiveness irritability of temper shedding of tears without occasion sleeplessness and even marked tremors The diagnosis of such infections is obviously made with much difficulty In the absence of a positive culture the only possible method of diagnosing the chronic form of the disease is the study of the combined results of a suitable allergic skin test opsonic index and agglutination tests

In describing the series of cases in Malta Debono (1939) divides his patients *into the intermittent and irregular types the undulant and* the malignant or septicemic types This follows the classification made by Hughes (1897) Debono s group of cases follows in the same general class as those studied in both Ohio and Iowa in the United States Debono notes that the intermittent and irregular types account for about 30 per cent of his cases and the clinical picture of them is characteristic The undulant type is the most frequent in Malta comprising about 60 per cent of the cases and in that country may be called the ordinary or typical brucellosis The characteristic feature is a series of pyrexal waves in which the temperature rises attains a plateau and gradually descends The pyrexal waves have no definite shape or length and are rarely so regular and so staircase like as the curve of typhoid fever A sharp drop of one or more degrees somewhere on the curve is common The waves may be as short as four days and as long as four weeks The average is about a fortnight The number of waves varies with each case the average being three or four but it may be as high as fourteen The waves may be separated from each other by an interval of apyrexia lasting a few days or even three or more weeks The apyrexia is rarely complete a low intermittent temperature normal in the morning and 37 5 to 38 C (99 5 to 100 4 F) in the evening is more frequent

The malignant or septicemic type of brucellosis is relatively rare in Malta as in the United States accounting for only about 10 per cent of cases The characteristics of this type which are quite similar to those of the fever as it is seen in other places are High continued fever which ranges between 40 and 41 C (104 and 104 8 F) and frequently reaches 41 5 C (106 7 F) Delirium acute toxemia and development of the typhoidal state are noted Bronchopneumonia is an almost constant accompaniment The face is suf

fused and cyanotic the tongue drv and brown the teeth covered with sordes the liver is usually enlarged vomiting is frequent and the urine which is scanty and loaded with albumin may be suppressed in the final stages The delirium is acute at first but soon gives place to apathy and bed picking The pulse which is over 120 per minute from the beginning becomes thready and intermittent typanitis develops and death takes place either from cardiac or renal failure in ten to twenty-one days All the symptoms point to severe septicemia The mortality is 40 per cent

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Other symptoms which have been observed in both the Iowa cases and those reported from Malta by Debono include pain which is not a serious symptom Usually the physician is impressed by the patient s almost complete freedom from pain Gastro-intestinal symptoms are rarely troublesome except in the moderately severe cases In Malta gastric disturbances are more fre quent At the onset and during the climax of the pyrexial waves there may be marked anorexia Epigastric tenderness is common and persistent vomiting is a bad prognostic sign Constipation is the rule but diarrhea may occur in the more severe cases and may give rise to confusion with typhoid fever

Enlargement of the spleen is one of the cardinal signs of brucellosis The splenomegaly usually persists throughout the course of the infection but the spleen may exhibit alternations in size growing and diminishing with the waves of pyrexia Symptoms referable to other systems such as the respiratory cardiovascular urogenital and nervous systems have been observed in both the Iowa and Malta series of cases

cal conditions No symptoms or signs may appear in chronic cases which even suggest a diagnosis of brucellosis There may be no history of an acute attack accompanied by a high elevation of temperature chills and sweats Both cultural and serologic examinations may remain negative throughout the course of the illness The only complaints occurring the first months of the disease may be exhaustion and occipital headaches Pains in the joints and back are common Many patients speak of vague gastric disturbances and pain in the right lower quadrant the latter sufficiently marked to suggest chronic appendicitis According to Huddleson the temperature in these cases is slightly elevated in the evening but may be subnormal in the morning and normal in the afternoon and even weeks may pass without notable fever Some patients gradually manifest neurologic symptoms such as mental depression apprehensiveness irritability of temper shedding of tears without occasion sleeplessness and even marked tremors The diagnosis of such infections is obviously made with much difficulty In the absence of a positive culture the only possible method of diagnosing the chronic form of the disease is the study of the combined results of a suitable allergic skin test opsonic index and agglutination tests

In describing the series of cases in Malta Debono (1939) divides his patients into the intermittent and irregular types the undulant and the malignant or septicemic types This follows the classification made by Hughes (1897) Debono s group of cases follows in the same general class as those studied in both Ohio and Iowa in the United States Debono notes that the intermittent and irregular types account for about 30 per cent of his cases and the clinical picture of them is characteristic The undulant type is the most frequent in Malta comprising about 60 per cent of the cases and in that country may be called the ordinary or typical brucellosis The characteristic feature is a series of pyrexal waves in which the temperature rises attains a plateau and gradually descends The pyrexal waves have no definite shape or length and are rarely so regular and so staircase like as the curve of typhoid fever A sharp drop of one or more degrees somewhere on the curve is common The waves may be as short as four days and as long as four weeks The average is about a fortnight The number of waves varies with each case the average being three or four but it may be as high as fourteen The waves may be separated from each other by an interval of apyrexia lasting a few days or even three or more weeks The apyrexia is rarely complete a low intermittent temperature normal in the morning and 37 5 to 38 C (99 5 to 100 4 F) in the evening is more frequent

The malignant or septicemic type of brucellosis is relatively rare in Malta as in the United States accounting for only about 10 per cent of cases The characteristics of this type which are quite similar to those of the fever as it is seen in other places are High continued fever which ranges between 40 and 41 C (104 and 104 8 F) and frequently reaches 41 5 C (106 7 F) Delirium acute toxemia and development of the typhoidal state are noted Bronchopneumonia is an almost constant accompaniment The face is suf

DIAGNOSIS

When the disease has been running for weeks and a temperature chart is available the diagnosis may be easy if the possibility of brucellosis is kept in mind It is in the first weeks that difficulties arise A list of diseases for which brucellosis has been mistaken would include practically every condition associated with fever The importance of laboratory tests in the diagnosis of undulant fever has been stated repeatedly Stitt states Once there is a suspicion of undulant fever one should try to confirm it by the more accurate method of agglutination tests or blood cultures rather than from clinical observations

Laboratory Diagnostic Tests

The laboratory procedures which are of value in diagnosis are the agglutination test the intradermal test cultural studies white blood cell and differential counts and opsonocytophagic tests The two of greatest value in differential diagnosis are the intradermal and the agglutination tests which are usually readily available Agglutinins can usually be demonstrated when the patient first applies for medical advice in infections with an insidious onset while in those with sudden onset they may not appear until the end of the second week or according to Simpson (1930) occasionally not until the fourth week Apparently it is true of brucellosis as of typhoid that infrequently the serum of an infected individual may persistently fail to show agglutinins It must always be remembered that a positive agglutination test may be related to a subclinical infection and not the present ailment of the patient A reaction of 1 80 is regarded as diagnostic in some cases the reaction does not rise above 1 40 and if this titer persists a diagnosis can be made with confidence Cases with a positive blood culture and negative serum agglutination reaction occur but they are exceedingly rare and it is dangerous to diagnose brucellosis in the face of a persistently negative serum agglutination reaction

Huddleson s rapid agglutination method used with whole blood can be carried out either at the bedside or in the office For the details of this method the reader should consult the original publication of Huddleson

Intradermal allergic tests as a means of detecting *Brucella* infections in cattle have been the subject of numerous investigations The literature on these tests has been reviewed by Huddleson (1939) The intradermal test in man may be positive in cases that have been exposed to infection and have acquired an allergy to skin test agents This is particularly true of packing house workers or veterinarians Thus the usual intradermal test must be interpreted with great caution and in conjunction with the results of cultural studies and agglutination reactions Huddleson believes that when the results of a suitable allergic skin test and the opsonocytophagic power of the blood in a phagocytic system are considered together they furnish the necessary information for diagnosis in most cases

The brucellergen test The protein nucleate fraction of *Brucella* cells has been used by Huddleson (1939) as an allergic agent for detecting *Brucella* skin allergy in human beings He has collected data in more than 20 000 indi

Loss of weight A progressive loss of weight usually takes place Emaciation is marked in severe infections and in those of prolonged though mild nature Rest in bed and an adequate diet usually counteract this There is a great loss of weight among ambulatory cases

LOCALIZED BRUCELLA INFECTIONS

Localization has long been recognized as characteristic of Brucella infections in animals In guinea pigs especially those inoculated with *B suis* we have repeatedly observed suppurative lesions notably arthritis osteomyelitis spondylitis meningitis orchitis and abscess of the spleen liver lymph nodes and other soft tissues In cattle brucellosis is typically a localized infection

With such lesions in animals the recognition of similar conditions in human beings has not been unexpected *Brucella* has been isolated from inflammatory lesions in various sites In many instances the finding of no other organism than this tends to support its etiologic role in others the causal relationship is still uncertain The localized lesions found in the series of cases studied in Iowa include a proved case of spondylitis Arthritis with detectable hydrarthrosis or swelling of the joints occurred in 2 per cent of the cases while tenderness in the region of the joints was not unusual and pain on active motion was a rather frequent complaint The specific nature of the hydrarthrosis was established by the isolation of *B abortus* from the joint fluid of one case Likewise *B suis* was cultured from a destructive eroding arthritis in one case involving the wrist joint Osteomyelitis involving the various long bones has also been present with or without an associated arthritis Endocarditis and pericarditis associated with a *Brucella* bacteremia were found in one case in *which other organisms could not be isolated from the blood stream* even after repeated attempts This complication associated in one case with pericarditis occurred in 1 per cent of the Iowa cases *Brucella* has been isolated from the bile aspirated by duodenal tube or obtained at operation by Amoss (1931) Gilbert and Coleman (1934) The organisms have also been obtained in cultures from subacutely and chronically inflamed gall bladders In one case *Brucella* was isolated from pleural fluid by guinea pig inoculation and in one case suppurative cervical adenitis suggesting a tuberculous condition yielded a pure culture of *Brucella* Cases with initial symptoms of cystitis and renal tuberculosis have been diagnosed as brucellosis through isolation of the organisms from the urine and positive agglutination tests *Orchitis was found* in 5 per cent of the males in the Iowa series Endometritis and abortion have been reported in the literature In 2 of the Iowa cases mastitis (3 per cent of the adult females) occurred as a symptom and sign of onset In several reported cases chronic subcutaneous abscesses have yielded *Brucella* in pure culture Meningitis and meningo encephalitis are less rare than has been supposed In the reports from the Mediterranean area it is evident that varied clinical pictures follow localized invasion of the central nervous system Roger (193°) and Roger and Poursines (1938) mention spastic progressive paralysis flaccid paraplegia and various meningeal reactions including that which simulated tuberculous meningitis

the diarrhea and tympanites as well as the sustained temperature and absence of sweats in typhoid fever taken together with a positive Widal test or the isolation of the organisms of *E typhosa* or *S paratyphosa* clarify the diagnosis Influenza tuberculosis malaria pyogenic septicemia subacute bacterial endocarditis acute rheumatic fever appendicitis and cholecystitis must also be differentiated In the case of tularemia it should be noted that the agglutination test may be misleading because of the phenomenon of cross agglutination *The agglutination titer in tularemia* is higher with *Tularense* antigen than with *Brucella* An intradermal test with brucellergen is positive in brucellosis but negative in tularemia

PROGNOSIS

In the Iowa cases there was a mortality of 3 per cent The duration of the infection is variable and cannot be predicted The prognosis therefore must be guarded especially if due to *B suis* A fair prognosis may be given with infections of *B abortus* In a study of 500 cases in the Malta series it was found that the duration of the febrile stage was one month in 20 per cent of the cases while in 25 per cent it was two months in 40 per cent three months and in 15 per cent more than three months While it was recognized that brucellosis varies in severity from year to year in Malta the mortality averaged between 4 and 5 per cent

TREATMENT

Treatment of brucellosis has to be divided into symptomatic and specific Symptomatic therapy includes general supportive measures and adequate nutrition for the patient A liberal diet is allowed in accordance with the patient s desire *Septicemic cases are best treated by external and internal hydro*therapy especially by the intravenous injection of glucose in normal saline to replace the liquid and salt lost in the profuse perspiration

Brucellin therapy has given very encouraging results and appears to be safe *Brucellin is a culture filtrate that has been prepared by* Huddleson and his associates (1936) For details regarding the methods of preparation and standardization the reader is referred to Huddleson s original article He has given the following directions as the result of nine years experience When a certain diagnosis of brucellosis has been arrived at an intradermal injection of 0 1 cc of *Brucellin* should first be given to determine the sensitiveness of the patient to the material If no marked systemic reaction is elicited within twenty four hours after the intradermal injection one may give 0 2 cc intradermally and 0 8 cc intramuscularly in the afternoon or evening If the total 1 cc dose elicits a local and systemic reaction characterized by a rise in temperature or a continuation of the rise in temperature during the following morning muscular pains chill and sweating a dose of the same size in the same manner should be repeated after an interval of 3 days If the second intramuscular injection produces a reaction similar to the first one the 1 cc dose should be repeated in the same manner after the same

viduals who were either normal or actively infected and found the test specific for detecting *Brucella* allergy Huddleson has called the substance brucellergen and has fully described the method of preparation and standardization of this test material

The brucellergen test is made by injecting intradermally 0 1 cc of brucellergen The reaction is observed at twenty four and forty eight hours after injection A positive reaction is characterized by circumscribed erythema edema and induration varying from 2 to 10 cm It may persist for seven days There is rarely if ever any necrosis or sloughing of the tissue at the point of local reaction In persons who are infected the local reaction may be accompanied by a more marked manifestation of the present symptoms and those who are hypersensitive will show a systemic reaction along with the local reaction Those who have not been sensitized to *Brucella* and who are probably susceptible to infection show no local or systemic reaction Often one sees in certain normal individuals during the first twenty four hours an erythema about ½ to 2 inches in diameter with no edema around the point of injection This is a non specific reaction A simple erythema has no diagnostic significance while edema and erythema 2 cm in diameter or more are positive

Brucellergen does not produce skin sensitiveness to subsequent skin tests One skin injection of brucellergen may give rise to *Brucella* agglutinins in a low titer in a small percentage of persons The agglutinins disappear in about sixty days

The opsonocytophagic test in brucellosis has been described by Huddleson and his associates (1932) The neutrophilic leukocytes in whole citrated blood of human beings who had recovered from brucellosis phagocytized *Brucella* cells in large numbers in a proper phagocytic system It was also observed that leukocytes in whole blood from actively infected cases showed a lower degree of phagocytic activity than did leukocytes in the blood of individuals after recovery and that the blood of those who had no past or present history of infection showed little if any phagocytosis For the method of performing this test the reader is referred to the original publications of Huddleson and his associates

A positive diagnosis of brucellosis therefore is made with certainty if the blood culture is positive and if the serum agglutination test is positive in dilution of 1 : 80 or more It is to be suspected of being positive if the agglutination tests are persistently positive in dilutions of 1 : 40 on repeated tests A single positive intradermal test must be interpreted with great caution and considered as diagnostic only if the agglutination test supports the intradermal reaction The intradermal brucellergen test may be considered as of diagnostic value especially when taken together with the agglutination test and opsonic index

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of undulant fever includes typhoid and paratyphoid fever The more rapid onset the dull toxic appearance of the patient

seem to indicate that sulfanilamide is specific for brucellosis On the other hand if the results in a large number of acute and chronic cases are summarized the conclusion is that sulfanilamide is not specific for brucellosis

Fluids are of importance as in any fever With profuse perspiration more than the daily cleansing bath is needed Tepid sponges for the control of temperature are indicated in a small proportion of the cases Medication to provide rest and relieve discomfort should be used

Focal infections with *Brucella* as in bones joints and different soft tissues must be given the medical and surgical treatment indicated

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interval This procedure should be continued until there is a tendency for morning and afternoon temperatures to remain subnormal during the intervals between injections As a rule at least 3 or 4 systemic reactions from *Brucellin* are required to bring the temperature to subnormal

If the first 1 cc injection fails to elicit a systemic reaction in the patient, it is useless to continue treatment at the time even with larger doses as such a patient has not yet developed a sufficient state of sensitization The dose may be repeated after an interval of 7 days and if the patient still fails to react further treatment with *Brucellin* should be abandoned

In the event that the first dose elicits a reaction and the second 1 cc. does not the third dose should be raised to 2 cc If no local or systemic reaction follows from the injection of these amounts the patient has become temporarily desensitized As a rule if a rest period of 7 days is allowed the state of sensitization will reappear If 1 or 2 injections of 1 to 3 cc are now given marked reactions may be obtained which are usually followed by recovery

If the systemic reaction from the intradermal injection is quite severe it is advisable to start the injections with 0 1 or 0 ^ cc. given intracutaneously If there is no severe systemic reaction following the injection of the smaller amount the succeeding dose at the end of 3 days may be doubled Each dose thereafter may be doubled providing the systemic reaction is not severe until 1 cc is reached Successive 1 cc injections may then be given intracutaneously and intramuscularly until recovery takes place

The afternoon rise in temperature in brucellosis is believed to be a sign of defense against the invading organism As a rule it is of short duration The injection of *Brucellin* at the beginning of the daily defense reaction or during the reaction serves to increase and prolong it If the defense reaction factor is taken into consideration when using *Brucellin* a more rapid recovery will be obtained

The contraindications to the use of brucellin are cardiac disease brain tumor kidney tumor pernicious anemia aplastic anemia epilepsy and diabetes

Other therapeutic methods have been suggested from time to time and among them serums and vaccines of various types have been tried Killed vaccine therapy was first employed by Basset Smith who considered it of value However his opinion has not been shared by others especially by the majority of physicians in Malta Rainsford (1935) has made a careful study of vaccine therapy in Malta and concludes that if recovery does not take place after two or three injections of vaccine its continued use is likely to result in more harm than good to the patient Vaccine therapy has been extensively used for brucellosis in the United States in recent years and while occasionally cases are reported in which it appears to have given remarkable results in general vaccines fail to affect the course of the disease in most cases

Other recommendations for therapy have been made especially in the use of sulfanilamide in acute brucellosis Promising results have been seen in a limited number of individual cases and on the basis of these alone it would

attack of typhoid fever and recovery of the organisms from the patients * and by the demonstration of the preventive value of the *E typhosa* vaccine

EPIDEMIOLOGY AND GEOGRAPHICAL DISTRIBUTION

E typhosa is world wide in distribution Paratyphoid A fever is more common in the Far East while paratyphoid B is more prevalent in Europe During the last war there were relatively few cases of typhoid fever as a result of administering typhoid paratyphoid mixed vaccine to the troops

E typhosa is distributed outside the human body in feces sewage soil water milk and other foods as a result of contamination directly with the discharges of a patient or of a carrier Fomites play an important part since the bacillus may live for weeks on blankets bedclothing and various articles contaminated by typhoid excreta The mode of conveyance of *E typhosa* may be either directly or indirectly from a previously infected person or by any route which permits the bacilli to reach the mouth and gastro intestinal tract

In the propagation of enteric fevers in the tropics as well as in temperate climates the essential factor is the individual who passes bacilli in his urine or feces or in both He may be either an acutely ill or chronically ill patient or a so called healthy carrier The chronic carrier may continue to pass typhoid bacilli in the excreta for years or even permanently The gall bladder is the seat of chronic infection so that the carrier at times suffers from cholecystitis or gall stones Some authorities believe that a person may pass typhoid bacilli in the excreta without having suffered from an attack of typhoid fever

The typhoid carrier is a danger to the community the degree of danger depending on his personal hygiene and also on the sanitary condition of the locality in which he lives

PATHOLOGY

The pathology of typhoid fever is related essentially to the small intestine Specific changes take place in the lymphoid elements chiefly at the lower end of the ileum although there may be a catarrhal condition throughout the small and large bowel The pathologic changes in the small intestine are most conveniently described in four stages

(1) *Hyperplasia (swelling) of Peyer's patches* The follicles are swollen and grayish white and the patches may project 3 to 5 mm or may be even more prominent During the first week the lymphoid tissue solitary glands and Peyer s patches become swollen The Peyer s patches appear as oval plaques extending lengthwise in the bowel Hyperemia may be observed microscopically at the beginning of the disease but later the lymphocytes increase in number and large mononuclear macrophages accumulate in the lymph follicles and in the reticulum and sinuses The normal structure of the lymph node is destroyed and the patch then consists of a dense mass of these large mononuclear cells with relatively few lymphocytes present This is the stage of greatest swelling

* Personal communication from Colonel J F S ler

CHAPTER XLVII

TYPHOID FEVER

Z T BERCOVITZ

TYPHOID FEVER IS AN ACUTE INFECTIOUS DISEASE CAUSED by *Eberthella typhosa* and characterized clinically by a continued but gradual steplike rise in fever in relationship to a slow dicrotic pulse Early in the disease there is a cutaneous eruption of small maculopapules The typhoid bacilli usually can be cultured from the blood stream during the first ten days or two weeks of the disease but later a positive Widal reaction and positive *stool culture develop The fever declines by lysis during the third week* when various complications may arise

HISTORICAL NOTE

In his Practice of Medicine Sir William Osler notes that Huxhan had observed the difference between the putrid malignant and the slow nervous fever In 1813 Pierre Bretonneau distinguished dothienenterite as a separate disease and in the same year Petit and Serres described entero mesenteric fever In 1829 Louis used the name typhoid to describe the same fever which at that time ravaged Paris and many other European cities Gerhard of Philadelphia was the first to state clearly the difference between typhoid and typhus fevers His studies appeared in the *American Journal of Medical Sciences* in 1837 Jenner and Murchison published studies between 1855 and 1862 in which they also clearly differentiated typhoid from typhus on clinical and pathologic grounds The discovery of the *Bacillus typhosus* by Eberth in 1880 clarified the picture yet further Following Eberth s work came the discovery of *Salmonella paratyphosa* A and B Pure cultures and the principal biologic features of *Salmonella paratyphosa* A and B were described by Gaffky in 1884

ETIOLOGY

Typhoid fever is caused by the *Eberthella typhosa* This fact has been proved by the development of specific immune substances in the blood of typhoid fever patients by the constant finding of the *E typhosa* in the blood and lesions by the ingestion of live typhoid bacilli by human beings with resultant

organ is not as important during the course of the disease as it is when the patient reaches the stage of carrier Then the gall bladder may become the focus from which the typhoid bacilli are constantly discharged into the feces

The Liver The liver is usually enlarged swollen and cloudy on section The characteristic typhoid nodules are found on microscopic examination

Heart and Blood Vessels No specific changes take place in the heart There may be degeneration of the myocardium Endocarditis is rare The heart is mottled as a result of fatty changes Microscopic examination reveals brown atrophy

Respiratory System A form of pneumonia may occur This probably represents an early localization of the typhoid bacillus in the lung—the so-called pneumotyphoid Later on in the disease pneumonia may develop either from the typhoid bacillus or more commonly from a secondary pneumococcus invasion Lobular pneumonia caused by terminal mixed infection is common in typhoid fever

SYMPTOMATOLOGY

The usual incubation period varies from seven to fourteen days or even longer It may be as long as twenty one days Five cardinal symptoms indicate typhoid fever

(1) The fever which shows a gradual steplike rise is remittent and ends by lysis

(2) The relatively slow dicrotic pulse that gives the usually characteristic picture of a pulse rate which does not follow the fever

(3) The toxic typhoid state

(4) Enlargement of the spleen

(5) The rose spots of typhoid usually found on the abdomen

The *typical onset* is gradual with prodromal symptoms of malaise anorexia pains throughout the body and limbs The tongue is coated the mouth dry and the patient thirsty The patient is generally apathetic Epistaxis is common There may be more or less generalized pain in the abdomen associated with diarrhea which is usually followed in a few days by constipation

Fever During the first week of illness there is a gradual steplike rise in temperature There are instances however in which the fever may rise suddenly and reach its peak in twenty four hours After a period of continued fever the high temperature begins to remit in the morning and finally terminates by lysis Continued fever of the remittent type which ends by lysis is characteristic of typhoid or paratyphoid fevers The fever may be high or low long or short in duration with remissions that may be marked or insignificant The onset may be gradual or sudden and the lysis slow or rapid

Pulse The pulse in typhoid fever is usually relatively slow in relation to the temperature It does not follow the temperature curve The pulse may also be dicrotic in character

Toxemia in Typhoid Toxemia is characteristic of typhoid The patient has a dull heavy stuporous appearance with flushed cheeks and moist face

and is due not only to the increase in the cell content of the patch but also to the edema which develops in the tissue This process of swelling reaches its height from the seventh to the tenth day of the disease It then undergoes either resolution or necrosis

(2) *Necrosis and sloughing* Vascular occlusion leads to anemic necrosis of the patch and the formation of a slough The necrosis in the severer grades often extends beyond the lymphoid tissue into the mucosa and deeply into the muscularis or even into the peritoneum In a mild case at the height of the swelling resolution may take place before the slough forms and the tissue may be restored to normal But more frequently the patch undergoes necrosis either as a whole or in part and then the slough forms The microscopic appearance of the lesion is unique in that practically no polymorphonuclear leukocytes are involved in the process The separation of the slough progresses from the outside toward the center and when the dead slough finally separates an ulcer is left

(3) *The stage of ulceration* Sometimes the ulcerations are superficial and involve only the upper layers of the mucosa But the usual typhoid ulcer extends down to the muscularis leaving a fairly clean floor covered with a thin gray exudate and a few shreds of fibrin Often the whole patch does not undergo necrosis instead the slough separates in large or smaller areas leaving irregular ulcers connected with narrow passages and separated by bridges of still intact mucosa The ulceration is more extensive toward the last few inches of the lumen

(4) *The stage of healing* The typhoid ulcer seems to be able to heal without scar tissue contraction and subsequent disturbance of bowel function

The important complications of the intestinal lesions are hemorrhage and perforation The hemorrhage is caused by erosion of exposed vessels in the area at the time of the separation of the slough Perforations the size of pin points are found at the base of small deep ulcers or in larger ulcerated areas where they may measure as much as 1 cm in diameter at the base

Lymphatic System The swelling of the mesenteric lymph nodes is probably the earliest lesion of typhoid fever The lymphoid structure and surrounding tissue become packed with mononuclear macrophages Small areas of liquefaction necroses result from vascular occlusion

The spleen is generally enlarged in typhoid fever and is extremely soft On microscopic examination the characteristic macrophages and pathologic conditions found in the lymph nodes and intestines are observed

Blood and Bone Marrow The most distinctive finding in the blood is the leukopenia During the first few days there may be mild leukocytosis with a relative increase in the lymphocytes especially in the large mononuclear cells The bone marrow undergoes changes similar to those described in the lymph nodes and spleen

Gall Bladder The organisms of typhoid fever reach the gall bladder very early in the disease and may remain there indefinitely A mild degree of catarrhal inflammation is usually present but the gross pathology of this

Relapses True relapses due to reinfection of the patient with *E typhosa* seem to have been definitely established These may occur after a few days of normal temperature The frequency of relapses varies in different epidemics The cause of relapses is not definitely established but Gay believed that they were due to overflowing of typhoid bacilli from their localized metastatic or ultimate foci in the body The gall bladder spleen and bone marrow are apparently the reservoirs for reinfection of the circulation

The course of true relapses is generally shorter and milder than that of the initial attack A new crop of intestinal lesions may occur the spleen may become enlarged again and rose spots reappear The duration may be from one to three weeks and in exceptional cases irregular fever may persist for several weeks

While it is generally believed that one attack of typhoid fever usually gives immunity for life a second attack may occur after an interval of months or even years

COMPLICATIONS

The most important and dreaded complications of typhoid fever are perforation and hemorrhage These complications are most likely to take place toward the end of the third week just as the temperature begins to show signs of decline

Perforation As there are usually no premonitory symptoms the onset of perforation is sudden and is accompanied by severe pain in the abdomen tenderness rigidity vomiting collapse accompanied by rapid pulse and a cold clammy perspiration *Hiccough is a symptom that may come slightly later in* the disease It may be persistent annoying and tax the patient s strength A sudden drop in temperature is characteristic of perforation and may mark the onset of collapse

Examination of the blood reveals leukocytosis a sudden increase in the polymorphonuclear leukocytes and a distinct preponderance of young non segmented forms When the perforation is pin point in size the onset of symptoms may be less sudden In these cases careful observation of the patient together with frequent blood counts gives a clue to the nature of the perforation

Hemorrhage Hemorrhage in the course of typhoid fever is usually massive and shows itself by the sudden appearance of tarry stools or by the passage of large amounts of blood from the bowel If the perforation is relatively low down in the ileum red blood may be passed from the bowel On the other hand if the hemorrhage comes from a point in the upper portion of the small intestine the patient may vomit dark blood In such cases the blood pressure falls suddenly the pulse becomes suddenly very thin and rapid and the blood count shows evidences of loss of blood The patient also shows marked restlessness

Involvement of the Liver and the Gall Bladder Typhoid bacilli are present in the gall bladder almost from the onset of the disease As a rule the presence

Enlargement of the Spleen Enlargement of the spleen is almost invariably present and is of great diagnostic value The enlargement is acute and the spleen is usually tender to the touch Enlargement may appear as early as the second or third day of the fever and the spleen may remain enlarged during convalescence *The acutely swollen tender spleen of typhoid fever however* bears no resemblance to the tropical splenomegalies of such diseases as malaria and kala azar

Rose Spots Rose colored spots usually appear in crops and may be seen during the first week of illness More frequently they appear during the second week They present a macular type of eruption that blanches on pressure and appears most frequently on the abdomen although it may be seen on other parts of the body

As the disease progresses the patient becomes weaker and may suffer from nausea and vomiting or from excessive thirst The abdomen may be either sunken or distended tympanitic and tender During this stage which usually comes in the second and third week constipation may be present *but diarrhea* may occur The patient becomes more stuporous the fever is high with morning remissions and the pulse may be very slow and weak Toward the end of this period great care must be exercised to avoid the danger of perforation of the bowel and hemorrhages the two most dreaded complications of typhoid fever These complications may occur simultaneously During this stage of the disease collapse of the circulation may take place or pneumonia or anuria may develop

At the end of the third week the morning remissions are more marked the fever does not reach the peak of the previous high point registered and lysis begins when the temperature falls more or less gradually This process usually *takes about one week thus giving the typical temperature curve of typhoid* fever The temperature usually reaches the normal level by the end of the fourth week

After the temperature begins to fall the patient begins to feel somewhat improved and by the time the fever has gone the patient may be distinctly improved At this time convalescence may begin and continue uninterruptedly The fever continues in some patients and as a result convalescence is prolonged Prolonged fever calls for a careful study of the case which should be examined for evidence of pneumonia pyelitis endocarditis cholecystitis or of failure of the typhoid lesions to heal Patients who have suffered from an acute attack of typhoid fever may become chronically ill They then become *chronic typhoid carriers* The passage from the acute to the chronic stage is usually very gradual Such patients may continue to pass typhoid bacilli in stools or urine for years and in some cases they will require cholecystectomy

The convalescent period is frequently lengthened by periods of fever which may last from one to four or five days This may be due to unwise diet undue excitement or to the development of a complication When these recrudescences occur there is usually danger of a relapse

disease or during convalescence Usually there is a rise in temperature that may be accompanied by a chill Pus is found in the urine and leukocytes may increase in number The pyelitis may be short lived or may persist for a considerable time Cystitis alone or associated with pyelitis may also occur and when it is present the bladder symptoms may cause considerable annoyance to the patient

Irritation of the meninges may occur at any time during the course of the typhoid fever In this case it is necessary to distinguish a meningismus from a true meningitis and lumbar puncture is the only means by which this dis tinction can be made Purulent meningitis may occur as a result of secondary infection with meningococcus pneumococcus or infection with the typhoid bacillus

Rarer complications of typhoid fever include *hemiplegia convulsions peripheral neuritis* and various *psychoses Conjunctivitis otitis media* and infections of various glands such as *mastitis orchitis thyroiditis* as well as *myositis* and *arthritis* are complications that follow in the wake of typhoid fever *Osteomyelitis* and *osteoperiostitis* occur but are not as serious when they are pure typhoid lesions as when they are complicated by other organisms

DIAGNOSIS

The diagnosis of typhoid fever rests on the demonstration of the typhoid bacilli in the blood feces or urine during some stage of the disease and upon the development of a positive Widal reaction While it is true that the clinical diagnosis of typhoid fever may be strongly suggested by the symptoms pre sented especially in the midst of epidemic conditions yet it is necessary to have positive evidence of the nature of the infection in order to complete the diagnosis Figure 66 shows the approximate positive findings with different laboratory tests according to the week of the disease

During the first week positive blood cultures are the most important singl factor in the early diagnosis of the disease Fortunately the percentage of positive cultures is highest during the first week of the typhoid infection With typhoid fever there is leukopenia with a relative increase in mononuclear cells

In addition to these laboratory data the clinical findings of the first week are suggestive These include the mode of onset which is usually gradual with a steplike rise in fever a slow pulse rate as well as headache somnolence and mental dullness Epistaxis is a prominent symptom in the first week of the disease

During the second and third weeks the characteristic rose spots of typhoid fever come out in crops starting from the eighth to the twelfth day At about the same time the enlarged tender spleen can be demonstrated

The laboratory findings of the second week include the development of a positive Widal reaction which usually appears from the eighth to the tenth day The culture of the feces should also become positive by this time The blood culture may remain positive for the first ten days to two weeks During the second and third weeks it should be possible to demonstrate the typhoid bacilli in the blood urine and feces and so to establish a positive diagnosis

of the organisms in the gall bladder does not give rise to inflammatory reaction but probably a low grade mild cholecystitis occurs not infrequently and runs its course without attracting much attention Only in a small percentage of cases does the inflammation become of sufficient severity to cause well-defined symptoms With conservative treatment the condition usually resolves itself in a few days

In rare instances the spleen may be the seat of complications and then perisplenitis infarct or spontaneous rupture may take place

Endocarditis and *pericarditis* are rare complications of typhoid fever *Myocardial insufficiency* may appear as a complication in the latter weeks of the disease Although the symptoms of cardiac weakness are a cause of great anxiety myocardial degeneration is a rare cause of death

Thrombophlebitis is a common and important complication of typhoid fever and it may be responsible for many of the irregularities in the fever Phlebitis rarely appears before the third week of the disease and most cases of this complication occur during the third or fourth week or during convalescence The veins of the left leg are most frequently affected but veins of both legs may be involved The onset of phlebitis is usually insidious and early localizing symptoms may be so mild as not to be recognized The local symptoms that identify the complication may develop only when occlusion is complete Small fragments may be detached from the growing friable clot and may become the cause of pulmonary embolism and infarction Thrombophlebitis is a distressing and serious complication and may cause death through pulmonary embolism extensive thrombosis into the abdominal veins or indirectly through exhaustion Treatment of the condition includes absolute rest in bed immobilization and elevation of the affected part and hot moist packs

Bronchopneumonia and *lobar pneumonia* are serious complications of typhoid fever In the case of bronchopneumonia the cause is the typhoid bacillus the pneumococcus or more commonly the pyogenic cocci The onset is usually insidious and is masked by the typhoid fever itself Respiration is increased the pulse becomes more rapid and cyanosis is present Lobar pneumonia is not a frequent complication of typhoid fever Pneumotyphoid is the name given to typhoid fever when its onset is characterized by pneumonia symptoms but in this case the disease runs its usual course The persistence of fever beyond the usual period the appearance of rose spots splenic enlargement and intestinal symptoms give the clue to a diagnosis of typhoid fever Lobar pneumonia complicating typhoid fever occurs during the second or third weeks of the typhoid fever or even later

Mild *infections of the urinary tract* occur in about one third of the cases of typhoid fever From the third week of the disease onward typhoid bacilli are passed in the urine which may become turbid as a result of the presence of the bacilli No other symptoms are usually present Bacilluria may persist for an indefinite period of time and the patient may become a chronic typhoid carrier *Pyelitis* is a complication that may appear at any time during the

duced over longer periods in dilutions much less than sufficient to establish a diagnosis of typhoid fever Agglutinins may persist for some time after vaccination and thus a positive reaction has to be interpreted cautiously

DIFFERENTIAL DIAGNOSIS

In the early stages of typhoid fever the differential diagnosis may be exceedingly difficult

Acute appendicitis must be considered It can be distinguished by its leukocytosis and increase in polymorphonuclear elements whereas typhoid fever has a leukopenia with relative lymphocytosis In this connection it should be noted that there may be an early slight leukocytosis in typhoid fever as well as in paratyphoid fever but the relative increase in the lymphocytes is suggestive of caution and the physician should make a blood culture which is usually positive during the first week Increases in the total number of leukocytes and polymorphonuclear cells which mark the variations in acute appendicitis are shown by day to day leukocyte counts while in typhoid the slight relative leukocytosis is soon lost and there is a steady increase in the lymphocytes

Paratyphoid fever cannot be differentiated from typhoid fever on the basis of clinical features but there are some characteristics of the two fevers that are helpful in differentiating them The typhoid fever patient is more toxic on the average the temperature is higher and shows smaller morning remissions the individual rose spots are smaller and the rash more scanty in typhoid fever than in paratyphoid Abdominal pain and distention are less severe in paratyphoid than in typhoid fever while the chances of perforation and hemorrhage are distinctly less than in typhoid The final diagnosis must rest upon the culture studies and agglutination reactions

Malaria has to be considered in any patient suffering from fever in the tropics It may be a complication of typhoid fever Intermittent fever with chills every other day or every third day suggests infection with the malarial *Plasmodia* but the diagnosis can be established by the demonstration of the malarial parasites in the blood smears The remittent and estivo autumnal types of malarial fevers may resemble the onset of typhoid fever Chills may be absent during the first days and the fever may persist with slight remissions and with increasing severity In such cases the diagnosis must depend on the positive blood culture for the typhoid bacillus or on the demonstration of *Plasmodia* in the blood smear

Typhus fever used to be readily confused with typhoid fever The onset of typhus fever is sudden with chills high fever rapid pulse great prostration vomiting severe headache and pain in the back and legs The typical eruption of typhus fever appears from the third to the fifth day is abundant and has a characteristic distribution There is a leukocytosis with typhus fever whereas the blood culture is negative for typhoid organisms

Relapsing fever is distinguished from typhoid fever by the sudden onset with chill and high fever nausea vomiting pain in the back and by jaundice which is frequently present The fever drops to normal in five to six days but

The diagnostic significance of the Widal reaction depends on previous vaccinations on the titers at which positive reactions are obtained and on the presence of H and O agglutinins A negative Widal reaction in one examination

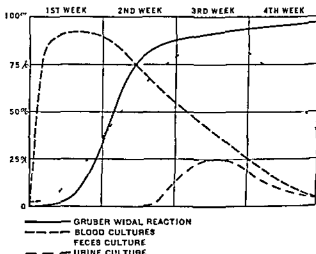


FIG 66 Typhoid fever Approximate positive findings with different laboratory tests according to week of disease in cases of about average duration The blood culture during the fourth week may be positive in about 25 per cent of the very severe cases in which fever persists through the fifth week (Park and Williams Pathogenic Microorganisms Courtesy of Lea & Febiger)

does not rule out the presence of typhoid fever Neither does a positive reaction *in low dilutions establish a diagnosis of typhoid since the patient* may have had preliminary vaccination For these reasons it is necessary to repeat the examination every few days in order to note the changes in the reaction Subsequent examinations giving evidence of a rising titer can be taken as reliable evidence of current infection with the typhoid bacillus A positive agglutination in titer of 1 80 is suggestive but a dilution of 1 160 is diagnostic

Whenever possible testing should be done for the presence of H and O agglutinins The floccular (H) agglutinins represent the flagellar elements while the granular (O) agglutinins are somatic The importance of testing for the presence of H and O agglutinins in suspected cases of typhoid fever is manifest since in some instances one of these agglutinins only may be present The O agglutinins are representative of group reactions while the H agglutinins are more specific *The O agglutinins are positive in lower titers than* the H agglutinins but they appear earlier than the H agglutinins A titer of 1 to 80 for the O agglutinins is diagnostic of the typhoid paratyphoid group The H agglutinins come later in the disease and are of diagnostic significance in dilutions of 1 to 160 or over The O agglutinin is more indicative of active infection while the H agglutinin may be produced by previous immunization through vaccination

Positive typhoid reactions have been observed from three months to one year after convalescence or after vaccination A slight reaction has been pro-

of the disease organism and the treatment of any complications that may arise

Barr has pointed out that circulatory collapse can be prevented in most typhoid fever patients if sufficient fluid for the maintenance of blood volume and for adequate diet is given This is best accomplished by the intravenous injections of 5 per cent glucose solution in normal saline although it may be necessary to resort to transfusions of whole blood or plasma to meet the needs of the patient A daily total of from 2 500 to 3 000 cc of fluids administered by the intravenous route may be required during the critical stages of the disease when the patient is so ill that he refuses to take adequate quantities of fluids and foods by mouth In making up the total amount to be given in any single day by intravenous injections the attending physician may wish to administer 500 cc of either whole blood or plasma as part of the total fluid intake In travenous therapy is necessary however only on the days when the patient s intake of fluids or food is inadequate

If whole blood is to be used it is of greatest importance that typing and cross matching should be done most carefully so as to avoid undesirable re actions in a critically ill patient

Plasma Transfusions

Plasma transfusions can be used to great advantage in typhoid fever especially if there is any question regarding the typing or cross-matching of whole blood There is no need for typing and cross matching of plasma This means that the blood of any individual can be used provided of course there is no syphilitic infection Plasma may be obtained in dried or concentrated form from some of the leading pharmaceutical houses Directions for dilution are included in each package and if these are followed faithfully there will be no untoward reaction when the plasma is administered to the patient When commercially prepared plasma is unobtainable when facilities for typing and cross matching are not available or when supplies of the correct type of blood are inadequate plasma may be prepared under field conditions The equipment required con sists of sterile flasks sterile rubber tubing with adapters and needles The blood should be withdrawn under sterile conditions and should flow into a sterile flask containing 60 cc of 3 per cent sodium citrate made up in sterile normal saline and sterilized The citrated blood is then allowed to stand in a refrigerator until the plasma separates from the corpuscles The plasma is with drawn with a sterile syringe and is placed under sterile conditions in a properly prepared bottle or flask for giving intravenously to a patient Care should be taken to exclude all corpuscles from the plasma The preparation of plasma may be facilitated if the equipment for centrifuging the blood is available This includes a centrifuge with bottles or tubes that can be sterilized and handled under aseptic conditions The citrated whole blood is then transferred under sterile conditions to the previously sterilized bottles or tubes and is centrifuged at high speed until the erythrocytes are completely separated from the plasma Under these conditions more plasma can be obtained

Plasma provides blood proteins and a certain amount of fluid it is sup-

after an intermission of a week to ten days there is a sudden relapse of the fever and a repetition of the symptoms that accompanied the first attack Positive diagnosis may be made by demonstration of the spirochetes of relapsing fever in the blood

At times *cerebrospinal* fever may have a gradual onset in which the temperature rises rather slowly and irregularly The headache is severe vomiting is frequent and by the third to fifth day the meningeal symptoms which include rigidity of the neck and positive Kernig s sign appear Blood culture is negative for typhoid bacilli but spinal puncture gives the characteristic reaction of cerebrospinal fever Some typhoid fever patients show meningeal symptoms but in typhoid it is in most instances a meningismus Invasion of the meninges with typhoid bacilli has been reported although it is very rare But in meningitis there is marked leukocytosis with a cell count of 15 000 to 30 000 and spinal puncture reveals a cloudy spinal fluid with polymorphonuclear cells containing the *Diplococcus intracellularis* In typhoid fever the spinal fluid is clear and the blood culture is positive in the first week a fact that should help to clarify the diagnosis *Tuberculous meningitis* has to be excluded in the differential diagnosis of typhoid fever as does meningitis caused by such agents as pneumococcus and streptococcus *Trichinosis* has been confused with typhoid fever in the early stages of the disease but leukocytosis with a high eosinophilic differential count and the development of positive intradermal and precipitin tests make the diagnosis clear Other conditions to be differentiated from typhoid include miliary tuberculosis tuberculous peritonitis malignant endocarditis syphilis pyelitis influenza septicemias and local infections acute exanthema pneumonia puerperal septicemia and acute enteritis

PROGNOSIS

The prognosis in typhoid fever depends on the severity of the infection and also on the complications The case mortality rate averages from 10 to 15 per cent The factors that influence the death rate of the disease include the age of the patient the type of outbreak the severity of local symptoms the presence of complications the treatment and previous antityphoid vaccination Typhoid fever is milder in individuals who have been vaccinated than in those who have not and the complications are also less severe

Typhoid fever must be considered a serious disease at any time and under any conditions The prolonged period of bacteremia fever and profound toxemia have a definite effect upon the health of the patient If incomplete recovery should follow an acute infection the chances of a prolonged illness are still greater In any event convalescence from typhoid fever is slow and the weakened condition of the patient predisposes him to secondary complications

TREATMENT

The treatment of typhoid fever is directed toward the support of the patient the maintenance of his fluid balance his nutrition the eradication if possible

TYPHOID DIET WHICH WILL FURNISH 3000 CALORIES

(From Coleman)

	Calories
Breakfast	
Farina (4 tablespoonfuls cooked)	100
Toast (1 slice 30 gm before toasting)	80
Cream 100 cc (3⅓ ounces) 20 per cent which is approximately the same as the top 4 inches from a quart bottle of milk that has stood at least six hours	200
Butter 8 gm	62
Lactose 40 gm (1⅓ ounces) To add lactose to milk boil 15 gm in 30 cc of water cool and add to milk	160
Sugar 20 gm	80
Coffee 1 large cup	00
10 to 10 30 A M	
Milk 200 cc (6⅔ ounces)	140
Cream 50 cc (1⅔ ounces)	100
Dinner	
Eggs 2	150
Potato 1 medium about	100
Bread 1 slice or roll 1	80
Butter 30 gm (1 ounce)	234
Apple 1 medium sized (pared and cored)	75
Sugar 15 gm (½ ounce)	60
(Potato baked served with butter Apple baked with 15 gm sugar and about 8 gm butter Some patients will eat more butter if the unsalted is used)	
3 to 4 P M	
Tea 150–200 cc	00
Lactose 50 gm (1⅔ ounces)	200
Sugar 5 gm	20
Cream 50 cc (1⅔ ounces)	100
Crackers 3 Uneeda or 2 soda toasted	75
Butter 8 gm	62
Supper	
Rice 25 gm (1 ounce) boiled	100
Milk 100 cc (3½ ounces)	70
Toast 30 gm (1 slice)	80
Butter 8 gm	62
Sugar 5 gm (for cereal)	20
Cream 60 cc (2 ounces)	120
Orange 1 sliced	100
Sugar 5 gm (with orange)	20
8 to 9 P M	
Cocoa 5 gm	25
Sugar 10 gm	40
Milk 150 cc (5 ounces)	105
Cream 30 cc (1 ounce)	60
Lactose 25 gm	100

portive and combats medical or surgical shock and plasma transfusion constitutes one of the most gratifying achievements of modern therapeutics

When the glucose and saline have to be prepared under field conditions the danger of reaction is greater than when sterilized ampules of these solutions are available Most reactions however can be prevented if the solutions are triple filtered and if scrupulous care is exercised in cleansing the rubber tubes used in giving the infusions Another method of preventing reaction in the patient is to give him a sedative before the infusion and then to administer the infusion very slowly The advantage of infusions of glucose in normal saline lies in the fact that vitamin C as well as vitamin B_1 can be administered with the infusion For the intravenous administration of vitamin C (ascorbic acid) the powdered drug in dosage of 1 gm (1 000 mg) should be dissolved in from 10 to 15 cc sterile distilled water This should be added to the 1 000 cc of sterile 5 per cent glucose in saline solution and should be allowed to flow into the patient with the infusion A total of 2 gm of vitamin C can thus be given daily Vitamin B_1 (thiamin chloride) in dosage of 100 mg can also be added to the glucose saline and allowed to flow in with each infusion

Diet

The function of diet in typhoid fever is to give adequate nutrition for the repair of tissue and for the maintenance of a metabolic equilibrium during the long febrile period of the disease As in the administration of blood and plasma transfusions dietary methods in typhoid fever are in striking contrast to former practice and they produce equally satisfactory results It is believed almost unanimously by clinicians that there is a reduction in the death rate when the patient has been given a full diet Certainly the severity of the symptoms has diminished since there is a decrease in tympanitis diarrhea and constipation in delirium and in stupor Bed sores are now rarely seen anemia is not as marked and there is almost no wasting of the patients While it cannot be proved statistically that the incidence of hemorrhage and perforation is less it is the impression of clinicians that it has not increased

Proper feeding constitutes the most important element in the treatment of typhoid fever and the main problem is to induce the patient to take as much food as is desirable Four thousand calories a day represent the optimum if loss of tissue is to be prevented but it is usually impossible to get the patient to take the full amount It is not essential to determine accurately the number of calories in the diet but the patient should be encouraged to eat as much as possible If diarrhea should occur it can usually be controlled by an adjustment of the fats and sugars in the diet Above all it is desirable to find out what foods the patient particularly likes and if these foods are at all practical to encourage him to eat them A liberal diet which includes a few simple and easily digested solid or semisolid foods is not harmful Coleman and his associates have shown that an intake of 60 to 80 calories per kilogram of body weight making a total of about 4 000 to 5 500 calories is necessary to obtain nitrogen and weight equilibrium The nitrogen balance can be maintained best by a diet with a moderate protein content the optimum being 62 to 91 gm of

and pass it through the meat chopper twice then place it in a pan to which has been added a small amount of water If the chopped meat is stirred into the water as it is being cooked it breaks up into relatively fine granules of meat and the beef extract with the meat granules is finally left This forms a very palatable base to which boiled rice macaroni or noodles can be added as desired Butter to suit the taste may be added

Fruit juices of all sorts form a means of administration of fluids white of egg and sugar Lemon juice grapefruit juice grape juice and at times orange juice are well accepted If on the other hand it is found that these cause an increase in abdominal distress or diarrhea they may be withheld temporarily or given in smaller amounts Strained tomato juice is another acceptable means of obtaining adequate vitamin C intake

Hydrotherapy

Various types of baths have been devised for the treatment of typhoid fever patients These vary all the way from Brand cold friction baths to the simple sponge bath while the patient is lying in bed The tepid sponge bath is most acceptable and can do no harm to the patient Other more energetic means of providing hydrotherapy have been advocated but caution and good judgment should prevail so that the patient will be spared as much shock as possible

Cathartics

BECAUSE OF THE DANGER OF PERFORATION NO CATHARTICS SHOULD BE GIVEN TO THE TYPHOID FEVER PATIENTS Cathartics must not be given to wash out the disease Indeed any cathartic medication must be avoided in typhoid fever If for any reason the bowels do not move evacuation of the rectum may be accomplished by the use of a very small amount (one pint) of normal saline given as a tepid enema This may be administered every second day at about the same time of day

Specific Chemotherapy

With the development in recent years of the sulfonamide group of drugs especially sulfanilylguanidine it is hoped that the course and severity of typhoid fever may be modified There is evidence that this drug acts on the *Escherichia coli* group of intestinal bacteria but sufficient evidence has not been accumulated as yet to warrant a definite judgment on its efficacy in the treatment of typhoid fever If the physician observes a few simple precautions he can administer the drug with the realization that while it may not be specific it will do no harm if ordinary care is exercised The dosage is 1 to gm every four hours for as much as a week or ten days It may be given as a powder mixed in milk or any other drink since it is tasteless and does not seem to upset the stomach It is necessary however to force fluids very actively while giving this drug because large amounts of crystals tend to form in the urine A daily urine examination must be made while the drug is being administered If at any time a heavy precipitate of crystals appears the drug must be dis

TYPHOID DIET WITHOUT MILK
(From Garton)

6 30 A M	Cup of hot coffee sugar 2 drachms (8 gm) 2 slices of zwieback or toast, butter
8 30 A M	One portion of oatmeal or Robinson s prepared barley with 6 buttered crackers saltines
10 30 A M	6 ounces of soup various kinds (180 cc)
12 30 P M	1 medium baked potato mashed and prepared with butter and salt 2 thin slices of buttered toast hot and 1 cup of hot weak tea with 2 drachms (8 gm) of sugar
2 30 P M	2 teaspoonfuls of pudding bread or tapioca 6 saltines
4 30 P M	2 ounces (60 gm) of rice farina or cream of wheat mixed with 1 ounce (30 gm) of butter and 4 drachms (16 gm) of sugar
6 30 P M	3 slices buttered toast
8 30 P M	6 ounces (180 cc) of soup

protein Carbohydrates are the most important source of energy and should constitute about one half the daily ration Fats are well utilized in all stages of the disease A diet made up largely of milk cream butter lactose eggs well cooked strained cereals meat broths either plain as consommé or to which have been added pureed vegetables such as beans spinach carrots peas potatoes rice is recommended The daily protein requirement may be obtained by the addition of from three to six eggs throughout the day to any of the formulas One of Coleman s diet lists is shown above and also one used by Garton

Milk and milk products are the most valuable single article of diet for the typhoid patient but if it is found that milk is distasteful to him it may then be necessary to resort to such articles as condensed milk whey junket ice cream custards cream soups creamed puddings and cream cheese

The carbohydrates also have an important place in the dietary of the patient and it is necessary for the attending physician to determine carefully which are best tolerated by the individual patient Thus it may be found that if glucose is not well tolerated milk sugar may provide a good substitute This carbohydrate is easily digested and does not ferment easily It has a caloric value of 120 calories per ounce Dextrin is another carbohydrate that is readily absorbed and well tolerated

Eggs are important in the dietary of the typhoid fever patient because they supply protein and fat in about equal proportions and have practically no undigested residue From four to six eggs may be given daily and they may be prepared in a great variety of ways such as soft boiled coddled whipped with milk or in one of the fruit juices

Meats in the form of meat soups broths beef tea bouillon and home made infusions are valuable but should be used cautiously especially at first and during the febrile period A simple way of preparing meat is to take lean beef

twice daily may be administered Fluids by mouth should be given sparingly in the first few days of massive hemorrhage from the bowel The use of a mixture of 1 part gelatin 3 parts lactose 30 parts water together with the juice of one orange is acceptable to the patient and can be given in amounts of about 3 ounces every or 3 hours This may be continued for two or three days after which a mixture of 16 parts soft gruel 14 parts milk 4 parts cream and 3 parts lactose can be served as an alternative to the gelatin mixture Slight modifications of this regime may be made at the discretion of the attending physician After a few days the patient s diet can be increased by the addition of milk and then by either a raw egg whipped into the milk or a soft boiled egg A palatable and nourishing food that is well tolerated by the hemorrhage patient at this stage is made by whipping ½ ounce (one tablespoonful) of malted milk powder into 5 ounces of milk into which a raw egg is carefully mixed and then a scoop of vanilla or chocolate ice cream is added Other foods that can be given to the patient include clear broths and soft strained gruels which should be given in amounts not exceeding ounces every hour or every two hours When there is evidence that the bleeding has stopped more soft pureed foods may be added to the patient s diet Amounts as well as variety may be increased Because the prognosis of the complication of hemorrhage should always be guarded the patient should be kept on a strict regime for at least three weeks to insure complete healing of the lesion There may be another hemorrhage at any time and for that reason vigilance is imperative

PROPHYLAXIS

The prophylaxis in typhoid fever represents one of the major advances in preventive medicine In Immunization to Typhoid Fever Siler and his associates point out that typhoid vaccine has been used by the United States armed forces for the past thirty years The organisms for the vaccine are killed by exposure to heat (56 C for one hour) in a water bath and 0 25 per cent tricresol is added to the saline suspension of organisms as preservative The Army vaccine has been standardized on the basis of 1 000 000 000 organisms per cc An initial course of vaccine is given to all military personnel and another course is given at the end of three years According to Colonel Siler three doses of vaccine are administered in each course at weekly intervals (minimum five days maximum ten days) and the dosage is 0 5 cc for the first dose 1 cc for the second and 1 cc for the third dose

The development of the mouse protection test for the detection and measurement of concentrations of specific protective substances in the blood has provided a technique for determining the duration of immunity following initial immunization and subsequent reimmunization The findings from a study of these tests indicate that when an individual is repeatedly immunized against typhoid fever the protective antibody content of the blood usually becomes stabilized at a high level where it remains over long periods of time The practical policies that Colonel Siler suggested as a result of his studies included the initial immunization with a virulent type vaccine three doses being used

continued A few individuals react to sulfanilylguanidine with fever and when this occurs the administration of the drug must be discontinued at once

There is no indication for the use of any of the other drugs in the sulfanilamide group It must be remembered at all times that the typhoid fever patient is toxic and that the addition to his regimen of toxic chemotherapeutic agents is unwise

TREATMENT OF COMPLICATIONS

Perforation Treatment of perforation usually taxes the physician s judgment to the limit When perforation is evidently of considerable size the shock may be so great in an already weakened patient as to make surgical intervention too dangerous to undertake Then the only things to do are to apply an ice bag to the abdomen and to administer fluids by intravenous infusion For this purpose 5 per cent glucose which can be administered in amounts of 2 000 cc. daily is most acceptable When transfusions of plasma are available they are life saving in combating shock if administered in amounts of 500 cc. either daily or twice daily Transfusion of whole blood in the same amounts is also salutary Absolute rest administration of morphine in large doses and application of heat to the body may lessen the shock to the patient and so enable the surgeon to operate

Peritonitis resulting from perforation is one of the most serious complications of typhoid fever Some cases have been reported of recovery following characteristic symptoms of perforation In most cases however generalized peritonitis proves rapidly fatal unless it is relieved by laparotomy But even with prompt surgical intervention the outlook is grave Only about 20 per cent of such cases recover but the operation is justified in face of the prospect of almost certain fatal termination without it

Some of the more recently discovered drugs especially sulfathiazole sulfadiazine and sulfanilylguanidine which belong to the sulfonamide group may be of value in the treatment of peritonitis resulting from perforation if they are available Sulfanilylguanidine is indicated in the treatment of perforation because it is of particular value against the *Escherichia coli* group of intestinal organisms

Hemorrhage Treatment in cases of hemorrhage must be prompt It includes absolute rest and the use of such sedatives as morphine codeine or sodium luminal Because morphine excites some patients codeine is to be preferred Nothing should be given by mouth Transfusions of whole blood and plasma are of greatest value 500 cc of plasma daily or twice daily or 500 cc of plasma alternating with 500 cc of whole blood may be used If available vitamin K given in amounts of from 2 to 4 mg twice daily by intravenous injection may prove life saving If vitamin C is available for intravenous or intramuscular injection it may be used in amounts of 1 000 mg twice daily

Fluids should be administered by clysis in preference to intravenous infusions to avoid the too rapid increase of the fluid volume without the addition of sufficient plasma proteins For the clysis normal saline in amounts of 1 000 cc

acquire the infection Prolonged and intimate contact is not always necessary to effect transfer of the infection There are many cases in which no contact can be traced although the patients live in an endemic area Exceedingly rarely cases the source of which cannot be ascertained occur in non endemic areas The channel by which the infection enters a new host is un known There is no good reason to regard any special form of contact such as sexual as of particular significance It is assumed that the infecting organ isms leave the patient through ulcerating surfaces of skin or mucous membrane or in some other way and in some equally obscure fashion infect a new victim Attempts at experimental infection of animals always have resulted in failure and the same is to be said of most if not all attempts to infect man experi mentally There seem to be a few well-established examples of accidental surgical infection of man Personnel of leprosy institutions rarely acquire the disease though this occurs more often than generally is recognized

There is some evidence that the purely neural type of the disease is not so likely to be transmitted as the lepromatous (nodular) type or the mixed form

There is a growing tendency which seems to be well founded to regard susceptibility as much higher in the early years of life than in the adult period

EPIDEMIOLOGY

Leprosy in the past has been of much more widespread geographical distri bution than at the present time when it is largely confined to the tropics and subtropical regions In most temperate climates it has disappeared or is declin ing Leprosy is not only very slow in its evolution in an individual but in a region as well While the prevalence of most infectious diseases in a community is measured by weeks and months leprosy usually requires generations and even centuries to go through a cycle of increase relatively steady prevalence decline and disappearance While this disease may be found anywhere it does not spread to an appreciable degree everywhere Thus in Europe leprosy spreads to a marked extent only in the Baltic and Mediterranean areas while in the British Isles and in Western Europe in general it spreads not at all or so feebly as to be negligible from the point of view of the health of the com munity The same thing is well illustrated in the United States of America where the disease spreads appreciably only in the states bordering on the Gulf of Mexico especially Florida Louisiana and Texas where enough new cases develop to keep the number fairly constant from year to year Just the reverse is seen in the northern and western states where the tendency is for the dis ease to die out for example the small focus chiefly of imported cases in the central northwestern states Minnesota Iowa Wisconsin the Dakotas has prac tically extinguished itself No matter how favorable the opportunities for contracting the disease may seem in these latter areas it is very rare for transmis sion to occur Imported cases of leprosy are occasionally detected in the north eastern states but cases originating in those regions are almost unknown This well illustrates that some factor other than contact with a leper is necessary to permit of transfer of the infection to others From what has been said it

Perhaps the most important date in the history of leprosy from the scientific point of view is 1848 when Danielsson and Boeck published their description of the disease next would come the discovery by Armauer Hansen in 1874 of the organism we consider the causative agent—one of the very early examples of a micro organism to be related etiologically to a clinical entity

ETIOLOGY

M leprae usually spoken of as the leprosy bacillus or Hansen s bacillus is by common consent regarded as the etiologic agent of leprosy although it never has fulfilled the requirements that should be met for establishing an organism as the cause of a disease The failure of anyone to present convincing evidence of the cultivation of the causative organism on artificial media and the inability to produce leprosy in animals are the reasons for the failure so far to prove the causal relation to leprosy of the organism that has been found in leprous tissue There are a number of conditions of animals bearing some similarity to leprosy but none is regarded as related etiologically to the disease in man though a disease found in wild rats and caused by the rat leprosy bacillus presents features bearing a fairly close resemblance to the human infection indeed a very few cases of alleged human infection with this organism have been reported

The classification * adopted for this discussion is as follows

Lepromatous type (nodular leprosy) in which the chief manifestations are due to changes in skin and mucous membranes

Neural type anesthetic maculo anesthetic leprosy in which the chief manifestations are referable to the peripheral nervous system

Mixed leprosy a form in which there is a combination of the manifestations of the preceding types

Tuberculoid leprosy is so named because of the resemblance of the microscopic pathology to that of tuberculosis It presents a form of leprosy that is often unrecognized or grouped under one of the preceding categories chiefly the neural type Tuberculoid leprosy is distinguished largely on the basis of the microscopic appearance of the lesions

Lazarine leprosy a form recognized by some authorities presents an early bullous eruption followed by necroses and ulceration often superficial

Transmission In the light of present knowledge leprosy must be regarded as communicable from person to person usually only after prolonged association between donor and recipient—beyond this we are unable to go with any certainty Apparently only a small percentage of adults in any population

* At the meeting of The International Congress on Leprosy Cairo Egypt 1938 a classification was adopted which is now in extensive use In this classification neural leprosy is indicated by N different degrees of advancement being indicated as N1 N2 and N3 While lepromatous leprosy is indicated by L different degrees of advancement are indicated as L1 L2 and L3 Subtypes of the neural type are anesthetic Na simple macular Ns and tuberculoid Nt Under this classification mixed cases are limited to those of the lepromatous type showing evidence of neural involvement which are designated as LN the degree of progress of the two elements being designated by numerals after the letters the L always coming first thus L1-N2 L3-N1

quently found and caseation usually is wanting The resemblance to the pathologic changes of syphilis may be very marked indeed opinions may differ between equally competent pathologists as to whether the lesion is that of syphilis tuberculosis or leprosy in a given specimen In the nerve trunks the perineurium is involved with secondary changes due to the presence of the infiltrating lesions around and between nerve fibers

Microscopically the tuberculoid type of leprosy shows a structure verging toward that of tuberculosis with epithelioid cells and giant cells of the Langhans type although the lesion is generally without necrosis and shows usually a scarcity or lack of acid fast bacilli According to McCarthy the tuberculoid type presents a histopathologic appearance of numerous sharply limited nodules of varying sizes made up of lymphocytes and plasma cells surrounding a central zone of epithelioid cells and Langhans giant cells

SYMPTOMATOLOGY

The incubation period of leprosy is longer than that of any other infection Two years is about as short an interval as elapses between exposure and development of first manifestations while periods of fifteen years or longer are not uncommon There are apparently well substantiated cases in which twenty five years or more had intervened but usually the incubation period will be from five to ten years

The clinical manifestations of leprosy fall naturally into two classes those affecting primarily the peripheral nervous system and giving rise to the neural or maculo-anesthetic type and those affecting chiefly the skin and resulting in the lepromatous (nodular) type Varying degrees of these two main types often are combined in the same patient resulting in the mixed form (Fig 67) perhaps more cases in which the disease is of considerable duration fall into this category than into either of the pure types Indeed some competent authorities believe that substantially all cases might be classified as mixed The tuberculoid type differs from the others chiefly in histopathologic findings especially in the absence or scarcity of bacilli and in the unusual locations of lesions These lesions are usually asymmetrical in distribution and often show a tendency to more rapid development than in the other types of leprosy

The objective manifestations of leprosy are said to be preceded often by febrile episodes One sometimes elicits a history of such occurrences but they rarely are observed by the physician Doubtless less frequently still are they recognized as related to the onset of leprosy since there is no distinguishing feature that would suggest this disease at that time

The indications of the onset of leprosy depend to some extent on the clinical type probably a third of the cases begin with manifestations referable to the peripheral nervous system with local tingling numbness and formications and with early impairment of sensory perception Perhaps about the same number of cases start with cutaneous eruptions which may be in the nature of erythematous patches the color varying in intensity or of circumscribed thickenings of the normally colored skin A considerable number of cases be

will be appreciated that the prevalence of the disease in a community depends to a large extent on geographical location Excluding imported cases the incidence will vary from zero to as high as several per hundred of the population the latter condition prevailing in certain regions in Africa today and comparatively recently the incidence was very high in some of the Pacific Islands. For reasons not clear leprosy in nearly all areas is much more prevalent among males than among females

In areas in which the disease spreads the tendency for multiple cases to occur in a family is striking, a goodly proportion of the children in a family having a leper member are likely to develop the disease Though leprosy is not hereditary there is some evidence that intra uterine infection may occur—probably very rarely The conjugal partner of a leper occasionally develops the disease usually due to exposure in an area of endemicity—very rarely this occurs elsewhere It has been suggested that at least in some parts of the world leprosy runs the course of a very slowly evolving epidemic which rises and declines with such gradual changes in prevalence that its epidemic nature is not recognized

PATHOLOGY

The essential lesion of leprosy results from the development of a granulomatous infiltration The pathologic changes involve chiefly skin and peripheral nerves Grossly the lesion is made up of faintly grayish or slightly yellowish granular looking masses These infiltrations may vary in size from the minute to nodular masses as large as the last joint of the thumb and may form sheets covering several square inches or even larger These changes cause the thickening of the skin and often form nodular masses that lead to disfigurement In advanced stages they may undergo ulceration especially in mucous membranes When these infiltrations occur in nerve trunks they give rise to the enlargements cylindrical spindle shaped or beaded that when found are so characteristic of the disease These infiltrations are frequently found in lymph nodes particularly in the glands of the groin and may be found in viscera especially in liver spleen testes and adrenals

The microscopic picture is not characteristic of the disease except for the presence of acid fast bacterial rods significant in size shape number (usually very abundant) and arrangement On the basis of histopathology alone the prudent pathologist will not go beyond a statement that a given section is compatible with leprosy unless of course characteristic organisms can be demonstrated in the tissue The most important cell in the leprous lesion is a large monocyte According to Black the acid fast bacilli are taken up by this monocyte which then becomes the classical lepra cell These are frequently called foam cells because of their vacuolar appearance Accumulation of these and other chiefly mononuclear elements leads to a thinning of the overlying epidermis with obliteration of the papillae so that the appearance is that of a smooth layer of epidermis overlying a tumorous mass The lesion bears some similarity to that of cutaneous tuberculosis but giant cells are less fre

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The neural type (Fig 68) progresses by intensification and spread of loss of sensation associated later with localized atrophy of muscular tissues The



Fig 6, Mixed leprosy Note loss of fingers and nodular infiltrations of face

latter usually is first noticed in the thenar or hypothenar regions and is caused by involvement of the median and ulnar nerves respectively or their branches Impaired sensation and atrophy in the extremities usually spread from the periphery toward the trunk When the condition is far advanced the hand assumes the deformity known as main en griffe or claw hand the metacarpal region often being extended on the forearm with the fingers flexed and the musculature of the hand and forearm showing much atrophy The nerves of the face may be involved giving rise to paresis or paralysis of the facial musculature especially the *Orbicularis oculi* In this type there may be large areas of anesthetic skin with a progressing reddish or brownish and often

slightly elevated border which may not be limited to the distribution of a single nerve

Skin changes may include either hypo- or hyperpigmentation and may be



Fig 68 Neural lep o y Note d f ity of hand with tropl c ul tio and upt n on b k and h l ls

early manifestations of the disease Cases occasionally are seen in which the appearance may bear a striking resemblance to the spots on a leopard The cutaneous changes often are confined to the covered parts of the body the shoulders hips thighs and arms being especially frequently involved In some instances readily detected loss of sensation may be of limited distribution and indeed doubtless at times may be absent This form of leprosy often presents trophic ulcerations especially over the joints of the fingers on the palms and on the soles in the latter location is found the so called perforating ulcer of the foot which often extends to necrotic bone All of these lesions are painless and the anesthesia may be so complete that it is a common occurrence for the patient to be unconscious of a serious burn This type of leprosy is not likely to prove fatal at least not until many years have elapsed Some cases never go

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or lost over the lesions but anesthesia is not a dominant feature as it usually is in the neural type

Cases of the mixed form of leprosy show manifestations of the two types in varying proportions indeed there may be a difference of opinion between equally competent observers as to whether a case is to be classified as mixed or designated as of the type showing predominant signs and symptoms

In the tuberculoid form two clinical features of importance are sharp demarcation of lesions from surrounding skin and asymmetrical distribution In some cases there is a tendency to acuteness giving an appearance similar to that seen in erythema multiforme

The lazarine form has a rapid onset in which there is a primary bullous eruption which may be superimposed on edematous infiltration or developed on an erythematous background Eschars form under which active ulceration progresses that may be so deep and extensive as to lead to the loss of part of a limb The lesions often develop on one or more of the extremities Usually the cutaneous changes bear little or no resemblance to those of the other clinical forms of leprosy and often other manifestations of the disease are said to be wanting Healing occurs with atrophy and scarring Acid fast bacilli are said to be abundant under the eschars and in the ulcers

Cutaneous lesions of leprosy of either type are often widely distributed but sheltered regions orbits axillae groins retro auricular areas and the middle region of the back of the trunk are likely to be spared

Fever is unusual in uncomplicated cases of leprosy but it occurs under two conditions in many cases

(1) Many persons suffering from leprosy pass through one or more attacks variously spoken of as leprous fever exacerbation of symptoms activation or leprous reactions These episodes are characterized by fever swelling of old and often development of new skin manifestations and general discomfort often with chills and sweats In neural cases during these attacks certain nerves may be extremely tender and neuralgic pain pronounced in the area of the peripheral distribution Some cases develop eruptions bearing a strong resemblance to erysipelas others like those of erythema multiforme or erythema nodosum These attacks may vary in length from a few days to a few weeks and usually subside leaving the patient little worse than before and occasionally even somewhat improved

(2) A protracted exhausting fever that often precedes the death of the patient is common possibly it is due at times or in part to secondary infection Perhaps the most noteworthy feature of the clinical evolution of leprosy is the extreme slowness it is exceptional to have marked changes occur in a period of a few months and often none for years Very rarely cases of the lepromatous type may progress with great rapidity

DIAGNOSIS

The making of a diagnosis of leprosy usually is of great importance since the recognition of the disease often means taking the patient from his usual surroundings his family and his normal mode of life The diagnosis may be

beyond atrophy and anesthesia of part of a hand or some other region Others may show nothing for years but skin discoloration and partial or complete anesthesia of one or more cutaneous areas indeed lesions may never progress beyond relatively trivial manifestations and consequently the diagnosis may be uncertain In such cases some collateral circumstance especially the disease clearly manifested in a parent a sibling or other close associate may aid in a diagnosis

It is in the neural form that we find the enlarged peripheral nerve trunk which is so often mentioned in clinical descriptions of the disease but not so often convincingly demonstrated This condition is best shown in the ulnar nerve above the elbow but may be demonstrated occasionally in other palpable nerve trunks However unless the examiner is satisfied that there is a definite circumscribed enlargement of a nerve he had better record it as negative It is easy for the inexperienced physician to persuade himself that an ulnar nerve is slightly enlarged and difficult for him to demonstrate this satisfactorily to a critical clinician Rarely abscesses caused by softening of infiltrated tissue are found on nerve trunks In some countries these abscesses are reported to be relatively common in the United States they are very rare

The neural type may lead to severe deformities as a result of bone changes the most common being the loss of fingers or toes or even of a hand or a foot The most characteristic deformities however are those caused by absorption of the phalanges This leads to shortening of the fingers without other obvious pathologic changes This condition may be so marked that the nail rests on a stubby finger remnant a half or a third of the length of the normal digit Rarely the condition proceeds so far that the nails or some of them appear to rest on the stump of the palm Doubtless similar conditions occur in the toes but do not attract attention so readily

The lepromatous (nodular) type of the disease usually begins with a discoloration of the skin most commonly an erythematous eruption which may fade to be replaced by a thickening of the skin or the latter may occur without a preceding rash The thickened areas may present the normal color of the skin but often are faintly grayish or yellowish brown they do not show pigmentations as deep as the ham colored areas so often seen in secondary syphilitic rashes The early lesions of this type often appear on the face cheeks eyebrows ear lobes and chin being favorite sites but they may develop on any part of the body and occasionally may cover large areas even as much as half of the whole surface The thickening of the skin may be diffuse or circumscribed (nodular) Rarely the face may be spared lesions being confined to less usual sites as one or both arms It is important to note that the nodules usually are in the skin not under it On rare occasions the lesions when advanced may undergo necrosis and be converted into purulent material When the infiltration on the face is pronounced the natural skin folds are accentuated In advanced stages this condition is known as leontiasis Hair of the scalp usually is not affected while that of the eyebrows often is lost generally earlier in the outer part In this type there often is involvement of mucous membranes especially those of the nose and larynx Sensation may be impaired

LABORATORY DIAGNOSIS

Sections made from tissue taken during life or at necropsy stained in the usual manner for histopathologic examination may give valuable information in connection with the diagnosis of leprosy but alone will rarely enable one to make an unqualified decision Sections stained for acid fast organisms in the manner usually employed to demonstrate tubercle bacilli may enable one to give a definite opinion if Hansen s bacillus is found even a negative result with properly selected and prepared tissue may be of great value

For the detection of the characteristic bacilli smears from tissues usually are much more convenient to secure prepare and interpret than sections indeed some experienced diagnosticians use them exclusively If the findings are positive for Hansen s bacillus the diagnosis is secure and even negative findings in suitably selected material will aid in ruling out leprosy

Smears are commonly made from cutaneous nodules or other infiltrations often from the nasal mucosa especially the septum and sometimes from ulcerating skin or mucous surfaces In any event the fixing and staining are the same as for tubercle bacilli Smears from cutaneous lesions are made by selecting an area of definite infiltration (thickening) grasping this between the thumb and index finger of one hand so as to throw the area into a fold or ridge which is compressed firmly to drive out the blood With a scalpel or safety razor blade (Gem type) held in the other hand an incision about one eighth inch in length or less is made into the area The edge of the cutting instrument is then used to scrape gently the edges of the tiny wound The tissue fragments and tissue juice so secured are transferred to slides fixed by heat and stained It is customary to make scrapings from several regions the ear lobes cheeks brow when infiltrated are favorite sites but the important point is to select areas where there is definite evidence of thickening though at times positive smears are obtained from locations that do not show gross changes Nasal smears made by securing material by means of a cotton applicator may suffice but usually it is desirable to use a nasal speculum and a head mirror so that suspicious or definitely infiltrated or ulcerated areas may be scraped Ulcers of the skin may be scraped with a dull instrument

No matter what site is chosen organisms if found must be characteristic in number size shape and arrangement to be of diagnostic significance They must be intensely acid fast bacillary or beaded some usually intracellular and many arranged in groups or bundles If these requirements are met there is rarely difficulty in arriving at a decision The term globi usually refers to clumps of acid fast bacilli which may be either intracellular or in the tissue spaces Organisms found in nasal smears especially must be characteristic as sometimes preparations from non leprous individuals will show a few acid fast bacilli usually plumper than Hansen s organism Rarely it may be necessary to make a comparison with known leprosy bacilli stained in the same manner and at the same time to be used as controls Some authors have laid stress on differential staining methods to distinguish various members of the acid fast group The serviceability of these methods is doubtful Usually the only

easy but in many early cases the expression of a definite opinion may need to be postponed until lesions have progressed far enough in their evolution to enable one to make a final decision It is much better to wait until evidence of the nature of the condition present is clear than prematurely to make a diagnosis that later may be found to be erroneous The value of our therapeutic and prophylactic measures is not sufficiently well established to require a final opinion at an early date in an obscure or doubtful case

In cases of the neural type gradual loss of sensitivity often reaching the degree of complete analgesia is the most constant finding It usually is associated with skin changes either hyper or hypopigmentation which are often followed by trophic changes muscular atrophy being the most obvious If with these or with some of them enlargement can be demonstrated in nerve trunks, the diagnosis can be reached readily In this type nerve biopsy has been employed but it is a procedure that hardly can be justified save in exceptional circumstances such as the insistence of the patient

In the lepromatous (nodular) type unless typical and advanced the final diagnosis usually must rest on finding the characteristic organisms in sections or in smears from a lesion Occasionally other conditions especially certain diseases whose chief manifestations are in or on the skin counterfeit leprosy in a manner that defies differentiation save by microscopic examination and even that may leave one in doubt In the present state of our knowledge of the tuberculoid type even if anesthesia is present one scarcely would be justified in making a diagnosis of this form save with the corroboration of characteristic histopathology In some cases there may be differences of opinion between equally competent observers after examining the same biopsy material

Extracts of lepromatous tissues and of certain bacteria and other agents have been employed with a view to evoking specific local or general reactions to aid in diagnosis but none of these tests has proved of established value

There are certain general considerations which although never conclusive in themselves may be of aid in reaching a decision as to whether a given case is one of leprosy The first of these is the age of the patient since this disease as generally recognized is unusual before ten and very rare under five years Careful examination of children of leprous parents may show suggestive manifestations at an earlier age The most important of the general considerations is the history of the former residence of the patient If he has lived in an area in which this disease is known to spread the probabilities are better that the case will turn out to be one of leprosy than if he never has been in such a region For example a person who never has lived anywhere save in the northern states of the United States or in the British Isles is most unlikely to develop leprosy whereas if he has ever lived in a part of the United States bordering on the Gulf of Mexico in Hawaii India or China or other endemic focus of this disease the chances of the disease being leprosy are much greater

Certain special studies of children of leprous parents have emphasized the fact that an early diagnosis of leprosy based on early lesions may be impossible but that later these manifestations may develop sufficiently to be easily recognized

nosis since generally confirmation is to be had through the demonstration of the characteristic organisms The following conditions frequently have given difficulty *Sarcoid* on the basis of history and clinical appearance may closely simulate leprosy but the absence of acid fast organisms in smears and often the presence of pathologic changes in the chest demonstrable by x ray examination serve to exclude leprosy Bone changes shown by x ray films may be present in either Fortunately the leprous lesions resembling those of sarcoid are likely to show acid fast organisms which facilitate their differentiation from this latter disease In sarcoid sensory changes are absent

Syphilis About half the cases of leprosy seen in consultation in the United States had been originally mistakenly diagnosed as syphilis This error is due not only to similarity of some of the skin lesions but also to the fact that serologic tests for syphilis often are positive in leprosy even in the absence of coexisting syphilis The distinction between leprosy and syphilis may be made by the absence of sensory changes in the latter and the more frequent presence of grossly infiltrating lesions in the former It is only the secondary eruptions of syphilis that are confusing but these are much more likely to be general in distribution than the manifestations of leprosy In syphilis there often is involvement of the mucous membranes which is not present in the early stages of leprosy The evolution of early syphilis is much more rapid than that of leprosy Alopecia so often seen in secondary syphilis is of rare occurrence in leprosy The constitutional symptoms of the former are helpful in reaching a diagnosis The syphilis like lesions of leprosy are likely to show acid fast bacilli Serologic tests are not of much aid

Lupus erythematosus may cause confusion which can be resolved only by repeated observation of the case and with the aid of microscopic examination The dilated follicles and the rather characteristic atrophy so often seen in lupus erythematosus on the face the usually brighter color the absence of sensory changes and the lack of acid fast organisms all point to this disease

Von Recklinghausen s disease (neurofibromatosis) may cause difficulty indeed has been found associated with leprosy The soft well circumscribed usually pedunculated character of the lesions the freckle like pigmentation and large brown areas of the skin found in this disease are helpful points

Cases of *multiple sebaceous cysts* have been seen which on first glance could not be distinguished from leprosy but careful examination made plain the true nature of the condition

Lupus vulgaris is said to be readily confused with leprosy but histopathologic studies should be of aid in differentiation In addition lupus vulgaris usually is confined to the face and neck while the manifestations of leprosy are often more widely distributed The apple jelly like character of the lesions noted on diascopic examination differs from any seen in leprosy In the parts of the world where leprosy is common lupus vulgaris is rare

Ringworm of the general surface which is common in geographical areas in which leprosy prevails probably needs to be considered in differential diagnosis as often as any other clinical entity The aid afforded by the recognition of acid fast organisms often is not available because many cases of ringworm

pathogenic organism that may be confused with the leprosy bacillus is the tubercle bacillus In any case where the differentiation is important it is best to rely on the inoculation of guinea pigs These animals are highly susceptible to tuberculosis but show no reaction to inoculation with leprosy bacilli The ulcers of the palms and of the soles due to or aggravated by trophic changes nearly always are negative for leprosy organisms

The number of smear preparations that should be made from a case suspected of leprosy before making a negative report depends on the individual examiner s judgment A dozen from any one case at one time should suffice but a positive smear has been found only after over a hundred had been negative A few words of caution are necessary in connection with the interpretation of smear preparations examined for Hansen s bacillus Rarely cases have been encountered in which acid fast bacilli so nearly typical of those found in leprosy have been seen that it was only on the basis of other evidence that this diagnosis could be ruled out therefore clinical and epidemiologic data must be considered in all cases

DIFFERENTIAL DIAGNOSIS

The neural type of leprosy and *syringomyelia* are readily confused—indeed a sure differentiation between the two may defy observers skilled in neurology and in leprosy Typical or advanced cases of either are readily recognized In general it may be said that in syringomyelia the neural manifestations sensory disturbances and atrophy are those of a central (cord) lesion segmental and bilateral In leprosy the manifestations are those of peripheral lesions localized or patchy anesthesia with no necessary relation to special nerve distribution There is dissociated sensory disturbance in syringomyelia pain and temperature perception are lost but not touch perception or only to a very slight degree while in leprosy all these are equally involved especially in advanced cases

There is said to be a difference between the two diseases in the order of the disappearance of the various sensory perceptions but in the experience of many this is difficult to demonstrate or to evaluate Syringomyelia lacks the skin discolorations seen in leprosy and never shows enlargement of the nerve trunks The neural manifestations in leprosy are more likely to be unilateral especially in early cases whereas in syringomyelia they usually are bilateral and often there are also nystagmus kyphoscoliosis increased patellar and Achilles reflexes and positive Babinski sign Syringomyelia usually develops later in life than leprosy

Family groups of neural disorders have been encountered in which on clinical and laboratory grounds leprosy could be neither affirmed nor disproved as concerned any individual case though well studied by competent observers this illustrates the difficulties that may be encountered in this field

Generally in cases in which the question is one of differentiation between nerve leprosy and other neural conditions biopsy and smear studies give little or no help

The nodular type of leprosy usually offers less difficulty in differential diag

life apparently often not being appreciably shortened by the disease Cases of either type or of the mixed form may be spontaneously arrested at any stage These especially if arrested at an advanced stage are sometimes referred to as burned out cases While data from different countries and institutions vary widely as to the proportion of cases dying of intercurrent illness in general probably it is safe to say that half of the lepers may be expected to die of leprosy and complications directly due to the disease Tuberculosis nephritis and pneumonia are frequent causes of death

TREATMENT

It is generally agreed that there is no specific for leprosy and that no therapeutic agent at our disposal is likely to influence the course of the disease materially Good living conditions sufficient well selected food suitable shelter and clothing doubtless add to the patient s chances of improvement but beyond this not much is to be expected Probably climate has no material influence on the progress of the disease in the individual case though of great importance so far as risk of transmission is concerned

Some authorities lay much stress on the benefit to sufferers from leprosy that may be afforded by the treatment of coexisting malaria syphilis dysentery hookworm infestations and other parasitic diseases Obviously it is desirable to treat any disease which may be cured or ameliorated whether the patient has leprosy or not but it is open to question whether the treatment of these incidental conditions will influence materially the progress of leprosy

Chaulmoogra oil and its derivatives especially the ethyl esters are used extensively and some clinicians of wide experience believe that great benefit is obtained from them others of equal experience see no advantage from their use Perhaps the majority of those who have used chaulmoogra oil and its derivatives feel that while these medicaments have no definitely curative value they may be of some benefit occasionally in some obscure manner Still others believe that these preparations should be administered to patients to keep alive a spark of hope that therapeutic measures may benefit them an attitude verging on that assumed when one administers a placebo

Chaulmoogra oil is so disagreeable to most patients when given by mouth that the intramuscular route of administration is growing in popularity but administration of the drug in this way may be attended by unpleasant local indurations or abscesses Coughing and respiratory embarrassment are consequences of hypodermic administration which occur occasionally and may be alarming If the oil is to be used it may be given by mouth beginning with 5 drops on sugar or in capsules after each meal The dose is to be increased by 5 drops per day until several cubic centimeters are taken daily but often in a short time the patient s tolerance is reached and the dose must be kept small or the drug discontinued If it is thought advisable to give the ethyl esters by intramuscular injection the dose may be started at 0 5 cc. and slowly increased to o cc weekly or twice weekly Some clinicians give preparations of the oil by injection into the skin lesions of the disease So far as trustworthy

like lesions of leprosy show few or none of these The following points are helpful in making a decision between the two diseases The areas involved in ringworm often are smaller than those of leprosy except when the former appear in the crural regions The ringworm like lesions of leprosy show a predilection for the scapular gluteal and thigh areas and in any of these locations may reach several inches in diameter or even cover a whole region and they are likely to be less distinctly circular in outline than the lesions of ringworm The scaliness and the papillary border so often seen in ringworm usually are lacking in leprosy The most important point of difference however is that this type of lesion in leprosy is almost certain to show anesthesia in some part a symptom that is lacking in ringworm indeed in the latter itching is very common The anesthesia may exist in the whole affected area but occasionally it is of so limited distribution that to detect it the most painstaking examination is necessary

The lesions of *vitiligo* and other leukodermic conditions may be similar to the depigmentations of leprosy and unless sensory changes can be demonstrated the diagnosis may need to be deferred until such changes occur or until it becomes clear that they are not likely to develop The depigmented areas in non leprous diseases are likely to be more sharply outlined than those in leprosy

Finally it must be admitted that in some cases the diagnosis between leprosy and certain neural and certain dermatologic conditions may be in doubt for long periods even after a patient has been observed by physicians with much experience

PROGNOSIS

Cases of the lepromatous (nodular) type or of the mixed form with predominantly nodular manifestations offer a much less favorable prognosis so far as possible recovery and of duration of life are concerned than do the pure or nearly pure neural cases The tuberculoid subtype of neural leprosy is said to offer a relatively favorable outlook

In any event the prospect of recovery in leprosy is not encouraging although it is not hopeless A proportion of the cases varying from 5 to ?5 per cent in different series may be expected to become arrested These figures vary widely largely by reason of what is considered to constitute arrest rather than from any great difference in the evolution of the disease in different parts of the world Thus it is obvious that if five years of freedom from signs and symptoms are required before a case can be considered arrested the number of relapses will be less than if one year is stipulated In any event a considerable number of apparently arrested cases will relapse in from a few months to many years One never should speak of a cure in leprosy but rather of arrest or of apparent recovery

Perhaps it would not be far wrong to say that the average patient with leprosy of the lepromatous (nodular) type lives from ten to twenty years from the onset while those with the neural type survive for much longer periods

mit such a reasonable course to be followed therefore we see lepers subject to rigorous even harsh measures in communities where they are not a menace to the health of others The reverse may occur in areas in which the disease is common enough to be familiar and where a case may be a source of danger in the latter instance people in general and patients themselves may be indifferent to the risk of the spread of the disease and suitable measures may prove difficult if not impossible to enforce In many countries the cost of attempts at control may be beyond the ability of the community indeed this is true of many regions in which leprosy is very prevalent Even in non endemic areas in which isolation is not required the victim especially if suffering from the lepromatous type or the mixed form should avoid exposure of children and contact with adults should be reduced as far as practicable Patients usually willingly observe these precautions

Confinement of the patient in a special colony or other institution is usually the best measure where isolation is demanded for the protection of the public health Where cultural and economic conditions are favorable agricultural settlements which are to a large extent self supporting are in operation Under some circumstances isolation in the home may suffice but as a general rule institutional care is preferable The detention need not be rigorous—visitors may be allowed and the patient may be permitted temporarily to leave the institution Indeed the opinion is expressed that if patients were allowed to come and go as they wished probably as much benefit would accrue to the community as by any other arrangement indeed this is the practice in some places Certainly the custodial prison like atmosphere of many institutions is not beneficial either to the patient or to the health interests of the community even though it is recognized that a more liberal attitude might lead to increased administrative problems In some countries where isolation has been found impracticable out patient dispensaries have been established in the hope of aiding in the control of the disease Segregation of the patient often is demanded in response to public sentiment or from motives of charity Much has been claimed for the success of segregation in controlling the spread of leprosy Usually these claims ignore other circumstances that may tend to limit the spread of the infection From the purely public health point of view too much is not to be expected from any measures and whatever possible benefit to the community may be achieved is likely to be a long time in becoming apparent—decades rather than years So far as concerns protective measures to be taken by an individual residing in a community in which leprosy is endemic the only advice is to avoid unnecessary association with lepers Those whose duties bring them in contact with cases should exercise ordinary precautions as to cleanliness

In communities in which the disease presents a public health aspect many problems must be met on the merits of the individual situation rather than by hard and fast rules The questions often are more social and economic than medical Thus in a family in which a case of leprosy is discovered it may be better to remove healthy children to a new environment keeping them under

evidence goes this procedure is of no more curative value than administration by other routes A formula for a preparation for hypodermic use (intramuscular or into the lesion) is as follows

Chaulmoogra oil	90 parts
Olive oil	10 parts
Benzocain	3 parts

The dose of this is from 3 to 5 cc twice weekly

Leprous fever and leprous reactions are to be treated symptomatically as there is no specific for either The erysipelas like type of reaction is said to be much benefited by sulfanilamide

The *complications* of leprosy naturally fall into two categories (*a*) Those diseases that are merely associated with leprosy thus we find lepers suffering from syphilis tuberculosis pneumonia nephritis malignancy surgical conditions and other diseases as do other persons These conditions need treatment without respect to the fact that the patients are suffering from leprosy (*b*) Complications due to the location or the progress of the lesions of leprosy itself *Nodules* chiefly on the face or on the ears may be so unsightly that one is justified in removing them if the patient so desires Nodular infiltrations of the conjunctiva or of the structures of the *eye* commonly lead to great impairment of vision and often to blindness Iritis is very common Treatment is not encouraging as witness the number of blind inmates in any leper colony Rhinitis and ulcerations of the nasal cavities need soothing sprays and lotions such as Dobell s solution Infiltrations of the structures of the *larynx* lead to the husky voice which is common among lepers and which may be followed by aphonia If the involvement of the vocal cords is extensive enough there may be difficulty of breathing a complication which finally reaches a degree that demands *tracheotomy* After this life saving operation a tube is inserted and the patient may live for several years in comfort but often he is not able to dispense with the tube *Ulcers* of the general surface due to necrosis of infiltrated areas are treated as are ulcers occurring with other conditions Ulcerations due to trophic changes such as the perforating ulcers of the foot may require the removal of carious bone and other necrotic tissue Finally a hand or foot may be so hopelessly disorganized that *amputation* is justified

PROPHYLAXIS

It will be evident from what has been said that measures for the prevention of the spread of leprosy should be taken with due regard for the facts that have been set forth in the preceding sections In areas in which experience has shown the risk of transmission to be so small as to be negligible no special public health measures should be necessary and patients may be permitted to continue their usual activities this is particularly true of neural cases In an area in which the disease spreads and therefore is a public health problem such measures should be taken as may offer any reasonable expectation of reducing the incidence of infection Unfortunately public sentiment often does not per

SECTION VII

NUTRITIONAL DISEASES

medical observation rather than to remove the patient from the home There is little danger of the disease spreading in family groups made up entirely of adults

The question of the marriage of lepers is usually decided on other than medical grounds but if the physician is consulted he should advise against it save in exceptional circumstances Sterilization of the male has been practiced The fertility of lepers is somewhat less than that of normal persons but by no means as low as generally is believed Children born to a parent suffering from leprosy should immediately after birth be removed to a non leprous environment Even in endemic foci only a small proportion of the previously healthy consorts of leprous mates acquire the disease—about 5 per cent in the Hawaiian experience Family contacts with cases of leprosy should be kept under medical observation so that new infections may be detected as early as possible

Probably no disease offers more varied problems for solution than leprosy —especially as respects public health measures The almost universal attitude of unreasoning fear of this disease on the part of the general public—and of some physicians—is not justified This disease needs to be dealt with intelligently and sanely as we deal with most infections in public health work Cases should be handled with due regard to stage type the personal problems of the victim and the potential danger to the community With respect to the last consideration it may be stated that probably in nearly all countries as many lepers are unrecognized or unknown to health authorities as are under sanitary supervision therefore an occasional additional case at large is not of great public health importance

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CHAPTER XLIX

INTRODUCTION

EDWARD B VEDDER

IN THE PAST THE TERM VITAMIN WAS DEVISED TO MEAN a substance essential for life and it is still useful to describe those substances of this class whose chemical structure is as yet unknown However the chemical structure of most of the vitamins is not only known but many of them have been synthesized Under these circumstances the chemical names are preferable to an alphabetical designation Accordingly in these chapters on the alphabetical letter deficiency diseases the chemical names will be used as far as practicable Since the alphabetical terminology of the vitamin has been in use so long it is advisable to present a brief summary of the different vitamins correlating the letter commonly used with the chemical structure

VITAMIN A

Although vitamin A has been synthesized and its chemical structure is known no chemical designation has been adopted for it

Vitamin A is taken into the body as such or formed in the liver from beta carotene which is accordingly known as pro vitamin A Beta carotene consists of two beta ionone rings united by a chain of four dehydrated isoprene residues In forming vitamin A beta carotene is split in half each half containing one beta ionone ring and two isoprene residues Accordingly it has been suggested that vitamin A could be called beta ionone diisoprenol or more simply beta ionone Other carotenes as alpha gama carotene and cryptoxanthin are converted into vitamin A These precursors of vitamin A however unlike beta carotene yield one molecule of vitamin A while beta carotene yields two

Beta carotene and other carotenes are found in abundance in green leafy vegetables and in carrots and from this source we synthesize our own vitamin A Natural A is found in greater or less quantities in milk butter egg yolk and liver particularly fish liver oils Halibut liver oil is several hundred times as potent as cod liver oil and jew fish liver oil may contain 600 000 U S P units per gm By molecular distillation in very high vacuum oils have been obtained of a potency of 3 000 000 U.S P units per gm These are used for experimental purposes only the usual source of vitamin A for therapeutic

from 1 to 2 mg daily or from 333 to 666 U S P units More is required during pregnancy and lactation Many people who receive less than this amount do not suffer from any obvious disease but they are not in the best state of nutrition and may lack vitality or may suffer from vague symptoms Since the deficiency is mainly caused by the limitation of diet to large quantities of white bread and sugar this fact has led to the enrichment of bread with thiamin niacin (or niacinamide) and riboflavin Thus it should be much easier to obtain the daily requirement of thiamin

THE B COMPLEX

The term vitamin B indicates the heat stable portions of the vitamin B complex Yeast contains all the factors of the B complex When yeast is autoclaved thiamin or vitamin B_1 is destroyed but the balance of the B complex or B is not so affected It has been found that animals fed synthetic diets containing adequate amounts of vitamins A D and in some cases C may be maintained in health and grow normally when autoclaved yeast together with additions of thiamin are included in the diet

Study of the vitamin P complex has yielded in addition to thiamin six vitamins which have been synthesized namely riboflavin niacin pantothenic acid pyridoxine para aminobenzoic acid and choline At least three other factors are known but so far they have not been synthesized

Riboflavin (Vitamin B or G) may be described chemically as 6 7-dimethyl 9 (1 d ribityl) iso alloxazine with the empirical formula $C_{17}H_{20}N_4O_6$ The synthetic product is readily available Riboflavin is a widely distributed yellow substance with a characteristic green fluorescence It is found in eggs milk and milk products meat products including liver kidney lean beef veal pork and leafy green and yellow vegetables

A Bourquin Sherman unit is the amount of riboflavin which when fed daily to rats will give an average gain of 3 gm a week during a test period of four to eight weeks in excess of gains in control rats without riboflavin One Bourquin Sherman unit is equivalent to approximately 2 5 micrograms of riboflavin The Jukes unit which is sometimes used is based on the chick and is approximately equivalent to the Bourquin Sherman unit

Rats deficient in riboflavin have areas of alopecia and cataracts have been produced by this deficiency in rats mice chickens and monkeys In dogs ataxia and degeneration of the posterior columns of the cord have been produced

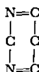
In man riboflavin deficiency is characterized by pallor of the mucous membrane of the lip at the angles of the mouth followed by maceration and superficial transverse fissures that extend downward sometimes for one half inch In addition to this condition called cheilosis there is also a fine greasy desquamation in the nasolabial folds on the alae nasi in the vestibule of the nose and on the ears A specific type of glossitis may also occur The color of the tongue is purplish red or magenta rather than the scarlet of nicotinic acid deficiency The papillae are large and flattened rather than atrophic. Fissures may occur There is also an ocular lesion consisting of superficial

purposes being fish liver oil The U S P unit is the same as the International Unit and is equal to the biologic activity of 0 6 microgram of pure beta-carotene A microgram sometimes called a gamma is one thousandth of a milligram Pure crystalline beta carotene as extracted from carrots or green plants is readily purchasable

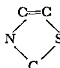
Deficiency of vitamin A results in failure of growth in animals and in keratinization of the epithelium When this occurs in the epithelium of the eyes it is called xerophthalmia Xerophthalmia has occurred in rare instances during wars or other circumstances of extreme food deficiency Urolithiasis in both kidneys and bladder has been produced in experimental animals and in man it is extremely common in parts of China and India where very little animal fat is consumed The earliest symptom in man is nyctalopia (night blindness) Keratinization occurs also in the epithelium of the pulmonary tree and leads to loss of natural resistance Cutaneous manifestations of vitamin A deficiency are not rare The skin becomes roughened by the presence of hyperkeratotic plugs in the follicles especially about the elbows and is commonly known as toad skin especially in the Orient The daily requirement of vitamin A for the human adult has been placed at 5 000 International Units In deficiencies five to ten times this amount (25 000 to 50 000 units) is given daily As much as 100 000 units have been used in treatment for short periods

VITAMIN B_1 (THIAMIN CHLORIDE THIAMIN HYDROCHLORIDE U S P)

Vitamin B_1 was synthesized by Williams and Cline in 1936 and was named thiamin It is composed essentially of a pyrimidine base



united to a thiazole



The hydrochloride is the form in which thiamin is usually obtained One International Unit which is the same as one U S P unit is equivalent in biologic activity to 3 micrograms of crystalline thiamin chloride

So far as natural foods are concerned thiamin is found in largest quantities in the external layers of grains such as wheat and rice in beans peas peanuts soybeans wheat germ lean pork to a less extent in lean beef and in lesser amounts in fresh vegetables It is present in large quantities in yeast

The amount of thiamin required in the diet bears a direct relation to the number of calories of carbohydrate food consumed and possibly to the weight but the minimum requirement for the average 150 pound man may be

Pantothenic Acid This vitamin was originally contained in the so called filtrate factor It was synthesized in 1940 by R J Williams and is now readily available as calcium pantothenate Pantothenic acid may be described chemically as alpha hydroxy beta-dimethyl gamma butyro-lactone combined with beta alanine

Liver and kidney of various species have been found the richest source of this factor followed by heart spleen brain pancreas tongue and lung Muscle tissue of beef lamb and pork contains lesser amounts

The deficiency of pantothenic acid produces dermatitis in the chick and pathologic changes in the spinal cord In rats the deficiency produces hemorrhages from the nose under the skin and in the adrenal cortex The requirement of the rat is about 50 gamma a day

Spies and his collaborators have found indications that this vitamin is also required in human metabolism but there is no information regarding the amount needed *Deficiency must occur very rarely in man* for pantothenic acid is widely distributed in foodstuffs

Pyridoxine Vitamin B_6 (factor I Adermin) has been named pyridoxine It is 2 methyl 3 hydroxy 4 5 dihydroxy methyl pyridine The synthetic product is available It is found in considerable amounts in liver legumes external layers of seeds cane molasses egg yolk fish and meats contain small quantities

Deficiency of pyridoxine produces dermatitis in rats and microcytic anemia in dogs No well defined condition is produced in man by the deficiency of this factor but Spies and his collaborators have found indications that human beings need some pyridoxine because certain patients responded favorably to a single 50 mg dose But there is no indication of the exact amount required by man Rats require about 10 gamma daily Certain cases of paralysis agitans have been markedly benefited by the administration of pyridoxine

Choline This vitamin occurs in the free state in most animal tissues and is widely distributed in plants It is a constituent of lecithin which is found in nervous tissues and in erythrocytes Lecithin is present in greatest amounts in egg yolk from which it is generally prepared but it is also present in liver heart and meat products Choline may be described chemically as hydroxy ethyl trimethyl ammonium hydroxide

Choline has been found essential to rats that are maintained on synthetic diets A deficiency of choline prevents growth and produces fatty livers hemorrhages and necrosis in the kidneys enlarged spleen and other changes Probably choline must be provided in the diet for the rat to synthesize lecithin When yeast of which this vitamin is a constituent is included in synthetic diets there is no deficiency of choline

Probably man never suffers from this deficiency since not only choline but lecithins are widely distributed in foodstuffs

Biotin It was found that rats that had been fed considerable amounts of egg white developed a specific dermatitis which was relieved by feeding them liver and other animal tissues The letter H was assigned to the unknown substance in these tissues that supplied this deficiency In 1940 it was shown that

vascularizing keratitis that is most easily observed with a slit lamp Circum corneal injection is commonly observed Superficial punctate opacities are common after the keratitis has developed All these lesions yield to riboflavin therapy

The human daily requirement of riboflavin is not known with certainty but on various evidence it has been placed at from 1 8 to 3 3 mg On a normal diet the excretion of riboflavin has been calculated to vary between 819 and 1 050 micrograms daily Daily therapeutic doses are from 5 to 15 mg by mouth in divided doses It can also be administered hypodermatically in normal salt solution

Niacin * (*Niacin Amide*) (Vitamin PI or P P Factor) It was found that liver extracts cured pellagra in men and blacktongue the canine analogue of pellagra in dogs Investigations showed that the active material in these extracts was nicotinic acid (niacin) and it has been found that pure synthetic nicotinic acid (niacin) cures both blacktongue and pellagra

Niacin is beta pyridine carboxylic acid the synthetic substance is readily available It has been found that the minimum requirement of the dog for the preventing of blacktongue is 0 13 mg per kg daily 1 5 mg per kg produces cures of pellagra in human beings The daily requirement of an adult has been estimated at from 15 to 25 mg and from 4 to 10 mg for children The amount of niacin in the blood has been found by one observer to vary from 0 160 to 0 89 per cent with an average of 0 73 per cent In the urine of healthy individuals from 1 0 to 2 0 mg of pyridine derivatives (calculated as niacin) were excreted In pellagra niacin could not be demonstrated in the urine until four doses of 50 mg each had been administered

Jolliffe has described an acute encephalopathy as a result of deficiency of niacin The condition is characterized by sucking and grasping reflexes cog wheel rigidities and clouding of consciousness Mortality has been reduced from 90 to 15 per cent by administration of niacin

In ordinary foods niacin is found in largest amounts in meats and meat products particularly in liver and kidney in milk cheese and eggs and to a much lesser extent in cereals The following analyses have been made

Substance	Nicotinic Acid (Niacin) Mg per 100 Gm
Beef liver	26–28
Beef kidney	17–18
Ham	8 8–10 4
Pork loin	5 3–13
Beef	3 8–10 2
Skim milk powder	4 3–6 2
Baker s yeast	50
Brewer s yeast	39–93 (six samples)
Liver extracts	210–450
Whole wheat	5 33
Home pounded ric	2 78
White corn	1 48

* Accepted as synonyms for nicotinic acid and nicotinic acid amide by the Food and Nutrition Board *J A M A* 118 819 1942

gen but no sulphur or phosphorus with a molecular weight of about 500 In obtaining this factor he extracted four tons of spinach Since yeast is a good source it may be placed in the B complex Many commercial canned greens are totally lacking in it Folic acid is present in animal tissues of which liver and kidney are the best sources The average weight of rats was increased by the administration of 50 gamma of folic acid but assays of the tissues suggest bacterial formation in the intestine

ASCORBIC ACID (VITAMIN C CEVITAMIC ACID)

After many difficulties because of its lability in natural sources vitamin C was isolated and identified by Waugh and King in 1932 and was synthesized the following year It was first called ascorbic acid to denote its antiscorbutic action Its empirical formula is $C_6H_8O_6$ This vitamin is available from a number of manufacturing chemists

Ascorbic acid is present in greatest amount in citrus fruits such as lemons oranges and grapefruit The juice of these fruits contains approximately 0 5 mg per cc. Tomatoes are nearly as active and considerable amounts are found in green leafy vegetables such as cabbage and spinach It is also found in lesser quantities in certain roots particularly potatoes onions and turnips Some ascorbic acid is also present in many other green vegetables An indeterminate amount of this vitamin is destroyed by oxidation in cooking and on standing (as in leaving citrus juices exposed to the air before using) or is leached out

The deficiency of ascorbic acid produces scurvy in guinea pigs in monkeys and in man Guinea pigs are the most susceptible and man the least susceptible

This vitamin is excreted in the urine in amounts depending on the amount consumed but this excretion ceases on a deficient diet The blood level of normal plasma may vary between 0 7 and 1 3 mg per 100 cc. But cases on a deficient diet have been observed in which there was no cevitamic acid in the blood for long periods yet scurvy did not occur Presumably the disease will not develop until the supply of the vitamin in the tissues is depleted

The human requirement of ascorbic acid has been variously estimated We know that scurvy was entirely eliminated from the British Royal Navy by the addition of 30 cc of lemon juice daily or about 15 mg of ascorbic acid to a completely deficient ration But this cannot be considered the optimum amount Some studies indicate that from 10 to 50 mg appear to be sufficient for the adult but when saturation of the body becomes the test from 60 to 100 mg appear to be required

VITAMIN D

The properties of vitamin D are found in ten different sterols The only two of major importance are the activation product of ergosterol known as calciferol (crystalline vitamin D) and 7-dehydro-cholesterol (animal vitamin D) Irradiated ergosterol dissolved in oil owes its antirachitic activity to its content of calciferol It is sold under the trade name of viosterol. Activated 7-dehydro-

this substance was identical with another unknown component called biotin Egg white inhibits the activity of biotin so that egg white injury is really biotin deficiency In September 1941 du Vigneaud and his collaborators announced the preparation of pure crystalline biotin to which they gave the empirical formula $C_{10}H_{16}O_3N$ S The structural formula was determined in 1942 Biotin is now accepted as another member of the B complex

Inositol There are a number of inositols I inositol is found in heart muscle and other animal organs but there is a more abundant supply of it in green peas and beans It is present in the free state and also in combination with phosphoric acid in the bran of various cereals The calcium and magnesium salt of this acid is known as phytin Deficiency of inositol is said to produce a specific dermatitis in mice (mouse alopecia)

Choline biotin and inositol interact in the prevention of fatty liver Best Hershey and Huntsman produced fatty livers in normal rats by feeding them a diet containing 40 per cent fat but fatty livers did not develop when lecithin was added to the same diet Subsequently they found that choline in the diet prevented the development of this condition

Nothing is known about the human requirements for biotin or inositol Presumably human deficiency does not occur because there is wide distribution of these substances in animal tissues and in cereals

The Anti Gray Hair Factor (Vitamin B_x) Several years ago A F Morgan found that certain strains of rats that were kept on special synthetic diets became gray in addition to degeneration of the adrenal cortex and early senility The condition was relieved by yeast some liver filtrates and rice polishings extracts No letter was assigned to this deficiency but reports appearing in 1941 indicates that this vitamin may be p aminobenzoic acid Further confirmation is required but in the meantime Sure has found that p aminobenzoic acid is a dietary factor necessary for the reproduction and lactation of rats Since this factor may be supplied by yeast it is probable that it should also be added to the components of the B complex Nothing is known about the human requirements of this factor

Vitamin B_3 and B_4 These vitamins have been described as essential for the growth of rats and pigeons Nothing is known of their chemical constitution or of their importance for man

FOLIC ACID

In 1940 a grass juice factor was discovered It was measured by the growth of guinea pigs on synthetic diets in which there were adequate amounts of the known vitamins This substance was found in greatest amount in the various grasses young white clover pea shells cabbage turnip tops and spinach Unlike cevitamic acid this factor was not injured by dehydration Animal tissues were a relatively poor source of it and old plants were less rich in it than young rapidly metabolizing plant tissues

In 1941 R J Williams who synthesized pantothenic acid announced the isolation of the factor which he named folic acid It is an acid containing nitro-

VITAMIN F (UNSATURATED FATTY ACIDS LINOLEIC ACID ETC.)

The letter F was originally reserved for bios a substance obtained in crystal line form which was required for the growth of yeast There is now some doubt whether this was a pure compound since several other definite com pounds including thiamin and biotin have been found to stimulate the growth of yeast

VITAMIN G

The letter G was originally reserved in the American system of nomenclature for the pellagra preventing vitamin which is now known to be niacin amide one of the factors of the B complex Vitamin G is now a synonym for riboflavin

VITAMIN K

Vitamin K was named from the Danish koagulation Two forms have been isolated from natural sources The product from alfalfa was designated K_1 It is identified as methyl 3 phytyl 1 4 naphthoquinone and it has been synthe sized Vitamin K is a metabolite of certain bacteria and appears in the lipoids of rotting fish meal It is described chemically as 2 methyl 3-difarnesyl 1 4 naphthoquinone These two vitamins are fat soluble More recently 2 methyl 1 4 naphthoquinone has been synthesized and called menadione and is furnished by commercial firms The sodium salts of phosphoric acid esters of certain naph th ohydroquinones are water soluble have approximately the same activity as K_1 and can be used hypodermatically

The natural vitamin is found mainly in green leafy vegetables alfalfa green leaves of cabbage spinach cauliflower tomatoes in unhulled rye and rice in liver egg yolk and in ham It is therefore widely distributed and deficiency in adults rarely occurs except from deficiency in absorption

Since the natural vitamin is fat soluble it is not absorbed if bile is absent as in obstructive jaundice in which hemorrhage often occurs Physiologically the deficiency of this vitamin results in inability of the blood to clot because prothrombin which is formed in the liver with the assistance of this vitamin is lacking This results in intramuscular and subcutaneous hemorrhages in the chick which has been used as the experimental animal in man particularly after operations and in hemorrhagic diathesis of the new born infant The prothrombin clotting time of the newborn may be greatly prolonged during the first few days of life a condition which results in bleeding If death does not take place there is spontaneous recovery as a result of bacterial action and production of vitamin K in the intestinal tract after the infant has begun feed ing This hemorrhagic disease of infants may now be prevented by administer ing synthetic vitamin K to mothers just before delivery especially if the mother s prothrombin clotting time is prolonged It may also be given to the infant as a preventive or a curative dose The dose is about 1 mg daily

In the case of liver disease prothrombin cannot be properly synthesized,

cholesterol is probably the material produced in the skin by the action of sun light and is the chief component of animal fats and liver oils Because fish oils are largely used in foods given to poultry this substance enters the yolk of eggs which except for animal fats and fish oils are the chief source of vitamin D

Vitamin D in either of these two forms prevents rickets and in suitable amounts cures the disease if it has already developed Since rickets occurs primarily in infants it may be assumed that the requirements of adults are comparatively low and can be provided by sunshine Except in summer sun shine is practically confined to that which falls on the hands and face It is true that osteomalacia develops in the adult as a result of deficiency of vitamin D but this is comparatively rare except among Indian women in purdah Such women get no sunshine at all

An indeterminate amount of vitamin D is consumed by most people in the food they eat Foods containing this vitamin include egg yolks animal fats and fish that have much body oil such as salmon sardines herring tuna and mackerel Since many people on deficient diets eat none of these foods and yet do not develop rickets or osteomalacia we are driven to the conclusion that the small amount of sunshine received is sufficient for practically all individuals except infants

The International Unit is the vitamin D activity of the international standard solution of irradiated ergosterol which is equivalent to 0 025 micrograms of crystalline calciferol The U S P unit is defined as equal in rachitic potency for the rat to one International Unit Standard U S P cod liver oil must contain at least 85 units per gm or 310 units per teaspoonful (4 cc)

VITAMIN E

This vitamin known as alpha tocopherol has been synthesized Its deficiency produces sterility in the rat and possibly in other mammals In the male de generation of the seminiferous epithelium occurs in the female there is de generation of the placenta with resorption of the fetus

Muscular dystrophy with degeneration of muscle fibers in the rat rabbit guinea pig and dogs has also been described as the result of this deficiency Far more important because of its bearing on the degeneration of the nervous system in beriberi is a recent study indicating that an extensive degeneration of peripheral nerve fibers and of the cells and fibers of the spinal cord develops as a result of a deficiency of alpha tocopherol The possibility that deficiency of this vitamin is responsible for habitual abortion in women has been con sidered but as yet this theory has not been definitely proved

Nothing is known at present about the needs of the human system for alpha tocopherol Complete deficiency must be rare for the vitamin is widely dis tributed in green leafy vegetables It is also found in large amounts in the embryos of grain and wheat germ oil has been used experimentally as a most potent source

N ci (t c f) Niacin am le (nicot ic cid am i)	5 35 mg (5 mg pe kg)	I r l m t m lk g t l l s	P ll g A t F j h l p thy	H C, HC, C—COOH, HC, CH, N
l t th d	—	Y t n b gg y lk l er m ats	D rm t t th h k	HO—C—C—C—C—N—C—C—COOH (H, CH, OH, O above; H, CH, H below; H H above, H H H below)
I yr l (B6)	—	La br	D rm t ti the t M rocyt c hypoch om c a m logs	CH_2OH, C, HO—C, C—CH_2OH, CH_3—C, CH, N
l m nobenzoi d (t gray h f ct)	—	F lt t f t f m y a t l	I s f ll k p gme t t h r f l l k rat d l f x	NH, C, HC, CH, HC, CH, C, O=C—OH
Ch l e	—	Y a t gg y lk l F nd oth r m l t s es a d pl ts	Fro th fa l	CH_2OH, CH_2—N $(CH_3)_3$, OH
Inos tol	—	I l a phyt be l pe	Neces ry f l t t M se l pe i	CHOH, HOHC, CHOH, HOHC, CHOH, CHOH

Table VII

SUMMARY OF THE VITAMINS

Vi mi	Adult Daily Requ e m t	Ch ef Sources	Effects of D ficie cy	Chemistry
A Beta i e	5 000 International U its	V tamin A butter milk egg yolk liver fi h liver oils B-ca ot ne (provita m ne A) yellow and green vegetables oranges pricots	Crowth fa lure Nyctalopia reduction of visual purple Kerat nizing metaplasia of eyes xerophthalm a Sk n toad kin. Sore mouth Resp ratory tract infect ons Ge to urinary tract urolith asis	[illegible]
Th B C m lex — *B* Th amin	2 mg	Yeast rice poli h gs pericarp and embryo of all grains l gum *nous veg tables milk* meat especially pork	A orex a growth failure Hypotoni ty and hypomot lity of gastro-intest nal tract lowered e cretion of gastric j ce Beriberi in man cardiac hypertrophy edema polyneuritis Polyneurit s in an mal	[illegible]
R bofl vi	1 5 3 mg	Egg yolk m lk, li r m ats l afy vege tables	Crowth fail re Alopecia in the rat Cataract in rats mice chickens monkeys Spa ticity and ge eral zed weakness n dogs Che los s glos tis keratit s in m n	[illegible]

F Alph tocc ph l	—	Fml ry f g a h t g rm d gree l es l tt p n h w t ces lf lfa	St l ty the m l l g t t semi f ro ep th l m th f mal d gen t f th fla ta with esorpt l the f l a M c l r dystr phy n th r t r b f t gu n p g	CH_3 H HO—C C CH CH_3 CH_3 CH_3 CH_3—C C C—(CH) CH(CH) CH(CH) CHCH C O CH CH
K		(ee l es f pl t — lfalf k f p h ce al l g t l les m l t ss es p trefy g fi h me l	I tr m scul d bc t h m rrh g n the h ck. H m h g m n (l t y th mb l fic cy)	O CH H (phytyl) CH O V t m K Phytyl h C C C C CC=CC CCCC CCCC CCCC O $C_{30}H_{49}$ (d f mesyl) CH O V tam n K D farnesyl h C C C C C C CC=CC CC=CC CC=CC CC=CC CC=CC CC=CC

TABLE VII — *Continued*

SUMMARY OF THE VITAMINS

Vitamin		Adult Daily Requirement	Chief Sources	Effects of Deficiency	Chemistry
The B Complex	Biotin (formerly H)	——	Liver kidney animal tissue	Dermatitis in rats resulting from ingestion of raw egg white	$C_{10}H_{16}O_3N_2S$
The B Complex	Folic acid (grass juice factor)	——	Grass yeast green *leafy vegetables*	Growth failure	——
Ascorbic acid (cevitamic acid) (vitamin C)		30 mg will prevent scurvy 60–100 mg optimum	Citrus fruits tomatoes *potatoes turnips and* leafy vegetables	Scurvy hemorrhage Odontoblast failure Demineralization of bones and teeth. Greater requirements in infections (protective against toxins)	O ‖ C—— HO—C HO—C O H—C—— HO—C—H H—C—OH H
D		400 Steenbock Units 1 100 International Units 400–800 U.S.P. units *for infants* Adults unknown	Butter egg yolk, milk fish liver oils	Rickets in children Osteomalacia in adults (Failure of endochondral bone formation with abnormal production of osteoid tissue at the epiphyses failure in calcification throughout all of the bone)	CH_3, CH, CH—CH—CH—CH—CH—CH_3 (CH, CH), H_2C, OH Vitamin D CH, CH, CH—CH_2—CH_2—CH_2—CH—CH_3 (CH), H_2C, OH Vitamin D_2

function *due to failure of co en yme action* The clinical phenomena depend upon the grade of vitamin depletion and the rapidity with which it is brought about The first part of this statement is apparently correct and is generally accepted but there must be other important physiologic activities of the vitamins The last two sentences would indicate that all the various phenomena of deficiency diseases can be ascribed to this cellular failure of co-enzyme action Beriberi for example would be caused by the accumulation of pyruvic acid from the breakdown of carbohydrate metabolism as a result of deficiency of diphosphothiamin (co-carboxylase) However it can readily be shown that this is false Neither the pathology nor symptoms of beriberi can be produced by either pyruvic acid or pyruvic acid salts

Further this ferment action does not account for the action of all the other vitamins for which no ferment action has ever been demonstrated Nor does it account for the highly specific nature of the pathology associated with every deficiency disease Deficiency of vitamin A produces squamous metaplasia of epithelial tissues specifically columnar epithelium becomes a squamous type Deficiency of thiamin produces cardiac degeneration as well as some nerve degeneration Inadequate amounts of nicotinic acid produce skin mucous membrane and mental changes in pellagra Riboflavin deficiency produces cheilosis and keratitis Dermatitis in rats results from insufficient pyridoxine A deficiency of vitamin C causes the failure of the intercellular cement or collagen to form with the resulting hemorrhages and softened bones of scurvy Vitamin D controls the calcium phosphorus metabolism of the bone structures In vitamin E deficiency there are both nerve degeneration and degeneration of the sexual organs (For a summary of the vitamins see Table VII)

Surely all these pathologic changes specific for each deficiency are not simply the result of improper utilization of carbohydrates because of failure of intra cellular coenzymes Merely to state the proposition is to formulate a *reductio ad absurdum* although at present we are quite unable to explain how the deficiency of each specific vitamin produces a specific pathology

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and hence no improvement in coagulation takes place as a result of vitamin K. Conversely if there is good absorption of fats and if a patient with prolonged prothrombin clotting time fails to respond to the administration of vitamin K it may be concluded that there is organic disease of the liver

Several methods of determining the prothrombin clotting time have been devised In certain cases whole oxalated blood is used but in most others oxalated plasma All methods depend on adding optimal amounts of calcium and thromboplastin so that the amount of prothrombin is the only variable Constant temperature and accurate timing are necessary By these procedures normal blood clots in from ten to twenty seconds and any delay indicates lowered prothrombin

Methods of assay for vitamin K are being developed but as yet there is no generally accepted unit

VITAMINS L_1 AND L_2

A recent investigation indicated that rats required these two vitamins to provide for lactation and the raising of young Nothing is known of their chemical composition or of the need for them that exists in other species

VITAMIN P

This substance is said to control capillary permeability *Szent Gyorgi* isolated it from lemon juice and called it citrin It may be valuable in certain cases of purpura caused by capillary fragility or permeability Vitamin P consists of crystals of two flavone flucosides hesperidin and eriodictol but it has not been synthesized

FUNCTION OF THE VITAMINS

Biochemists have found that certain of the vitamins combine with other substances to form ferments which are involved in all cell metabolism and particularly in the provision of energy from carbohydrate food which is first oxidized and then decarboxylated In the case of the B vitamins this action has been described by U P Sydenstricker as follows

Nicotinic acid is the chemically active fraction of the co enzymes diphos phopyridine nucleotide (co enzyme I) and triphosphopyridine nucleotide (co enzyme II) which are essential to the intermediate metabolism of glucose Thiamine is the reactive portion of diphosphothiamine (co carboxylase) Riboflavin is similarly the active portion of the yellow ferment of Warburg which is ubiquitous in cells and is thought to function as an intra cellular respiratory ferment

Thiamine nicotinic acid and riboflavin are thus concerned with the con tinuous processes of cellular nutrition and respiration and while they function in part as activators which are continually regenerated they are also components of co enzymes which are used up and require constant replacement All these vitamins are probably normally present in all cells The symptoms and signs of avitaminosis may be regarded as results of chemical disturbances of cellular

susceptible Eijkman also found that whole rice or highly milled rice together with the polishings removed in the milling did not produce the disease In 1901 Grijns found that polyneuritis gallinarum could be prevented by the addition of a legume to the diet of highly milled rice It was not therefore the ice per se but the deficiency of something removed from the rice in the process of milling that was responsible for the production of the disease Obviously the protective substance was in the polishings

By 1911 at least three sets of investigators had obtained crystalline materials that would cure polyneuritis produced by rice feeding In the Philippines this was accomplished by Vedder and Williams in Japan by Shimamura and Okake In England Funk on finding that the substance contained nitrogen and that it was necessary to life called it vitamine This name became immediately popular and gave Funk more credit than he deserved for none of these investigators had as yet the pure vitamin as it was subsequently called It was not until 1926 that Jensen and Donath isolated the pure vitamin Their work was confirmed by R R Williams who also developed methods of extracting the substance in large quantities He also succeeded in synthesizing it in 1936 when he named it thiamin

Vitamin Deficiencies Numerous observers have noted the prompt recovery of the heart and the dissipation of edema following the administration of pure synthetic thiamin chloride This has also been found to be true of infantile beriberi which has been described as the purest form of B_1 deficiency

The matter is not so simple when we come to consider the cause of the changes in the nervous system That thiamin deficiency may produce a certain degree of nerve degeneration can hardly be doubted Satisfactory results following the administration of thiamin have been reported in the polyneuritis caused by alcohol now known to be due to deficiency of B_1 rather than to the toxic effect of alcohol Spies and his collaborators have reported the same satisfactory results with thiamin in the polyneuritis developing in pellagrins after the acute symptoms have been relieved by niacin Thiamin was originally thought to be the antineuritic vitamin chiefly because of the phenomenal recovery from polyneuritis gallinarum of birds after they have been given an adequate dose of vitamin B_1 Although these birds were clinically cured when they were killed it was found that they still had degenerative changes in the nervous system indeed it could hardly be expected that these advanced changes could be repaired in a matter of a few hours which is all that is required for the clinical cure Further in experimental animals that have been subjected to deficiency of thiamin alone in carefully prepared synthetic diets the nerve degeneration produced is very slight

All observers have found that administration of thiamin to advanced cases of dry beriberi produces no phenomenal cure Some relief is commonly experienced in subjective symptoms but the administration of thiamin alone does not completely restore the patient s ability to walk for this restoration involves a long process of months even when the patient is given a diet that is complete in all food essentials

CHAPTER L

BERIBERI

EDWARD B VEDDER

BERIBERI IS A DISEASE RESULTING FROM FAULTY METABolism and is directly caused by the deficiency of thiamin and of several other vitamins Among Orientals this deficiency is usually produced by the too exclusive use of decorticated or polished rice but it may be caused equally by the excessive use of white wheat flour and other carbohydrate staples Clinically beriberi is characterized by degenerative changes in the nervous system including a multiple peripheral neuritis which may exist alone but is often combined with generalized edema and serous effusions and by a tendency to cardiac hypertrophy which frequently results in cardiac dilatation and sudden death

ETIOLOGY

The dietary origin of beriberi is now generally accepted although all investigators have not yet agreed as to the *modus operandi* Many observers from the time of Braddon who first focused attention upon rice as a cause down to the very distinguished investigator MacCarrison as late as 19 8 believed that as a result of the deficient diet a toxemia was produced which was responsible for the pathology and symptomatology of beriberi

There have been many epidemiologic observations incriminating overmilled rice as the cause of beriberi In the Malay States Braddon pointed out that the Tamil laborers who ate only parboiled rice never suffered from beriberi although it was very common among the Chinese who lived among them and ate only overmilled rice Cured rice or parboiled rice is boiled before husking and as a result not only is the husk more readily removed leaving the external layers fairly intact but it is also quite effective in preventing beriberi even when it is machine milled This is probably because the process of cooking the whole grain distributes the vitamins in the external layers at least to some extent through the entire grain

Polyneuritis gallinarum Eijkman in 1897 found that fowls fed exclusively on highly milled rice developed a paralytic condition closely resembling dry beriberi It was subsequently shown that pigeons and other birds are even more

known as kakke in China the Malay Peninsula the East Indies and the Philippines In China and India the disease is common in the south but rare in the north In North China millet is the staple diet and in the north of India whole wheat is used Beriberi is also constantly present along the east and west coasts of Africa especially among contract laborers In South America the disease is commonest in Brazil but it also occurs in Venezuela Panama and the West Indies In the United States it has been reported from Louisiana where rice is grown and is consumed in large quantities Small outbreaks have occurred in insane asylums and jails in the United States and England In Labrador and Newfoundland it is associated with an almost exclusive diet of white wheat flour While Europeans are not immune to the disease they do not develop beriberi in the Orient although surrounded by natives who are suffering from the disease

PATHOLOGY

The pathology of beriberi may be discussed under three heads cardiac pathology anasarca and degenerative changes in the nervous system

Cardiac Pathology

Death is caused by cardiac hypertrophy and sudden dilatation and failure of the right side On postmortem examination the heart is found markedly hypertrophied and dilated especially on the right side the chambers being filled with blood which is usually fluid The valves are normal and there is no gross degeneration In 1898 Ellis in 123 necropsies in cases of beriberi found that the average weight of the heart was 379 gm and that the right side in nearly every case was much enlarged During the same period 204 hearts from patients dying from other diseases averaged 255 gm McLaughlin and Andrews describing the same condition in infantile beriberi state Probably the most striking and constant change is found in the right heart Its musculature is coarse and firm and forms much the larger part of the organ even in the contour of the apex Its trabeculae and papillary muscles are prominent while its cavity is enlarged The wall of the right ventricle may measure from 5–7 millimeters in thickness while the left measures only 3–5 millimeters The weight of these hearts averaged 34 1 gm with a maximum of 54 gm while in death of similar infants from other diseases the average heart weight was 20 gm with a maximum of 3 gm

The average weight of the heart among Japanese beriberi patients has been given as 368 gm while the maximum of normal hearts is 300 gm The enlargement is most pronounced in the right chambers and the right auricle is huge in size with a paper thin wall through which the dark blood within may be seen As a result of the back pressure from this right sided failure there is chronic passive congestion of the liver spleen kidneys and intestines Punctate hemorrhages are often found subpleurally and in the stomach and duodenum The vessels in the stomach and intestine are dilated and hyperemic

Wenckebach who had wide experience with beriberi thought that from the

Beriberi is produced usually by a rice diet and highly milled rice is not deficient in thiamin only but also in vitamins A D and E the common fat soluble vitamins Nearly all the fat of rice is in the external layers and is removed in the *process of milling Rice is also deficient in some parts* of the B_2 complex although these may not be deficient in the diet if the subject eats sufficient fish or other animal protein with his rice

A number of investigators have shown that a considerable degree of degeneration in the nervous system can be produced in various experimental animals by diets deficient only in vitamin A in the vitamin B complex or in vitamin E

Beriberi is therefore a complex deficiency and further scientific progress will depend on administration of all these vitamins to cases of dry beriberi and on observation of the results Fortunately all these vitamins except A may be readily procured in synthetic form and pure vitamin A can be obtained by molecular distillation

The amount of thiamin required by any individual depends primarily on three factors the proportion of carbohydrate in the diet the activity of metabolism and the relative ability to absorb thiamin Varying amounts of thiamin are therefore required by different individuals But when an individual adopts a diet deficient in thiamin physical impairment begins as soon as his reserve stock of thiamin is depleted

As a result of various experiments it would appear *that man has little* ability to store thiamin Symptoms caused by a diet very deficient in thiamin may appear as early as five days On a diet containing an inadequate amount of thiamin (50 I U) although symptoms of beriberi develop true beriberi (nerve degeneration enlarged heart edema) may not appear for 147 days But on a diet of rice true beriberi may appear in ninety days in laborers

EPIDEMIOLOGY

Beriberi may occur in any race but it is usually confined to the races that eat rice The disease may occur at all ages and in both sexes but as a rule it is commoner in men There is good evidence that hard muscular labor favors its development on diets that would be sufficient for sedentary workers Among women beriberi is more frequent during pregnancy and subsequent lactation Infantile beriberi of breast fed babies is a common cause of mortality in Japan the Philippines and probably in other Oriental countries where beriberi is endemic Here again a diet sufficient for women under ordinary circumstances is inadequate during pregnancy and lactation Beriberi is chiefly confined to the poor the coolies and contract laborers although well to do people may develop the disease if they place unwise restrictions on their diet For example in 1935 Kepler reported a case of beriberi in the United States in which the patient s diet was restricted to raw starch

GEOGRAPHICAL DISTRIBUTION

Beriberi is endemic in all countries where rice is used as the staple article of diet Thus it is a serious cause of disability and death in Japan where it is

known as kakke in China the Malay Peninsula the East Indies and the Philippines In China and India the disease is common in the south but rare in the north In North China millet is the staple diet and in the north of India whole wheat is used Beriberi is also constantly present along the east and west coasts of Africa especially among contract laborers In South America the disease is commonest in Brazil but it also occurs in Venezuela Panama and the West Indies In the United States it has been reported from Louisiana where rice is grown and is consumed in large quantities Small outbreaks have occurred in insane asylums and jails in the United States and England In Labrador and Newfoundland it is associated with an almost exclusive diet of white wheat flour While Europeans are not immune to the disease they do not develop beriberi in the Orient although surrounded by natives who are suffering from the disease

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Wenckebach who had wide experience with beriberi thought that from the

beginning the entire heart was enlarged This enlargement increases more or less rapidly but the failure affects the right side only

Weiss and Wilkins found that in the beriberi heart the fibers of the myocardium showed hydropic degeneration and an increase in the intercellular substances but an unaltered water content The conductive fibers were also involved in this process On electrocardiograms of these cases they found changes in the T waves and prolongation of the electrical systole (Q-T) Similar changes have since been noted by a number of investigators R D Williams and his collaborators at the Mayo Clinic studied 10 patients who were receiving a diet deficient in thiamin Electrocardiographic abnormalities were found particularly diminution of the T waves as well as some diminution in all complexes although none of these subjects had any cardiac enlargement Changes in the electrocardiogram are apparently the earliest manifestation of cardiac damage from this deficiency The apparent hypertrophy is therefore caused by degenerative changes and the heart is weaker than normal

In a study of circulatory changes Weiss and Wilkins made technical measurements of the circulation in 13 cases The most significant finding was that patients with enlarged heart rapid heart rate gallop rhythm dyspnea generalized edema low vital capacity and elevated venous pressure had a normal or increased velocity of blood flow and a low arteriovenous oxygen difference This differs they pointed out from other types of organic heart disease in which there generally exists a direct relationship between the degree of congestive failure and the slowing of the blood flow The rapid blood flow warm extremities flushed color and increased arterial pulse pressure indicated a generalized arteriolar dilatation and an increased capillary pressure

Anasarca

The proportion of wet cases will vary in different outbreaks of the disease When edema occurs it is noticed first in the legs and extends later to the thighs which cause the legs to feel stiff and makes walking difficult While often confined to the limbs edema may become general although the face is rarely affected Edema of the lungs may be found in 30 per cent of the cases Serous effusions are usually found most frequently into the pericardium less frequently into the pleura and peritoneum The effused fluid is clear and greenish yellow in color In 189 recorded cases pericardial effusion was reported in 145 pulmonary edema in 78 hydrothorax in 24 and ascites in 14 The amount of fluid in the pericardium varies from 50 to 200 cc in hydrothorax from 50 to 2 000 cc.

Until very recently there has been no satisfactory explanation of the fact that some cases of beriberi are dry and others are wet At present my explanation is that the edema depends on the failing heart combined with the increased pulmonary pressure

Clinicians are now reporting cases of cor pulmonale The mechanism is a sudden dilatation of the right side of the heart which usually follows in this country a sudden obstruction of the pulmonary artery by an embolus or

thrombus Like beriberi its onset is explosive with extreme suffocating dyspnea cyanosis and pain The symptomatology given for cor pulmonale could be taken word for word as the description of a case of beriberi with acute cardiac failure Further we have here the explanation of the serous effusions of wet beriberi which have not been satisfactorily explained previously

Degenerative Changes in the Nervous System

The changes in the spinal cord noted in necropsies of cases of beriberi are not usually grossly apparent Bentley reported 19 such necropsies in which he found the brain and its membranes congested and the spinal cord congested and softened The lesions of the cord were so gross as not to require the use of the microscope to see them he added for in some only a few hours after death the cord was soft and diffluent with hemorrhage marked congestion and extensive edema quite sufficient in themselves to cause all the symptoms My observations go to prove that it is a cord lesion which involves both sensory and motor functions of central origin a subacute inflammation of the spinal cord and its membranes Most observers have not noted such gross changes or have attributed them to postmortem changes but in recent years I have found the same condition in rats subjected to diets deficient in vitamins especially in the B complex

In any case there can be no doubt as to the microscopic changes which have been reported by all observers Degeneration of the medullary sheath has been demonstrated in scattered fibers in all tracts of the cord but especially in the posterior columns as well as in both anterior and posterior nerve roots In some cases the axis cylinder is fragmented Degeneration of the nerve fibers is best demonstrated by the Marchi method and degeneration of the cells by Nissl or Giemsa stains The changes found in the cells in the anterior horn and the posterior spinal ganglion which include swollen and dislocated nuclei and loss of the Nissl bodies which break down into a powdery mass depend on the length of time the disease has lasted In more advanced degeneration this powdery mass almost disappears and the vacuolation of the cell follows with rupture of its membrane and fragmentation of its processes Similar changes have been found in the ganglion cells of the medulla and pons In most cases these changes are not to be regarded as complete degeneration or as the death of the cell from which there would be no recovery but they do indicate a very complete exhaustion of the affected cells and it is to be expected that the fibers originating from them will show degenerative changes

Some degree of degeneration may be found in any peripheral nerve but since the legs are first affected in beriberi changes are most marked in the sciatic n rve and its branches When these are stained by the Marchi method it is observed that degeneration of the myelin sheath is constant and may affect the majority of the fibers in some part of their course the myelin being first blackened later broken up into black balls or beads and eventually disappearing When this occurs the axis cylinders may show a coiled appearance and in certain cases are fragmented or atrophied But usually the greater number

appear normal even when the medullary sheath shows advanced degeneration Similar degenerative changes have been found in the cranial nerves particularly the phrenics and vagi and in the recurrent laryngeal nerves thus causing the characteristic aphonia It is especially to be noted that degeneration of the sympathetic system has been demonstrated in branches of the cardiac plexus the splanchnic nerves and branches of the solar and renal plexuses It may be of interest to state at this point that almost identical changes have been found in the nervous system of fowls dying of polyneuritis gallinarum

The muscles supplied by these degenerated nerves particularly of the leg and thigh are markedly atrophied with consequent loss of cross striation and shrinkage of the sarcoplasm which are often combined with cloudy swellin or fatty degeneration In very advanced dry cases the muscles of the arms or even the trunk are similarly atrophied Such muscles are exceedingly tender to the touch so that the patient flinches at even the gentlest examination

SYMPTOMATOLOGY

The symptoms of beriberi may be divided into three syndromes correspond ing to the pathologic alterations as follows

(1) Symptoms referable to degeneration of the nervous system
(2) Symptoms produced by the generalized edema and serous effusions
(3) Symptoms depending on the cardiac hypertrophy and dilatation

The clinical picture of any individual case of beriberi depends on the pro portions in which these three types of symptoms are blended Cases in which the symptoms are dependent on degeneration of the nervous system are called dry beriberi Cases in which the tendency to edema is most pronounced are called wet beriberi Cases in which the heart is seriously affected early in the disease and in which sudden death may occur with little warning have been called acute pernicious beriberi

The onset is generally insidious For days or weeks the patient is readily fatigued and experiences a heaviness of the legs stiffness and soreness of the muscles and increasing inability to walk When he does exert himself he may suffer from palpitation and dyspnea Gastro intestinal disturbances are com mon and are manifested by anorexia discomfort after eating with either con stipation or diarrhea In both birds and dogs the earliest symptom of thiamin deficiency is anorexia and impairment of motility of the stomach and intestine

On examination it will be found that the muscles of the calves are painful when squeezed and there may be some loss of sensation over the distribution of the anterior tibial nerve and some paresthesia such as burning of the feet Slight edema of the feet and legs is common

The patient may remain in this condition for months or years with alternate improvement and exacerbation of symptoms the changes probably depending on slight changes in the diet This condition has been described as rudimentary beriberi and is frequently found in mothers whose children have died of in fantile beriberi But more often the patient gradually becomes progressively worse and the symptoms of marked peripheral neuritis appear sometimes com

bined with rapidly progressing edema and increasing cardiac incapacity The muscles become weaker and at the same time acutely sensitive so that the patient flinches when examined The extensors of the foot are affected first resulting in foot drop and this is followed by wasting of the muscles of the calf then of the muscles of the thigh In more serious cases the arm muscles atrophy a little later the muscles of the forearm going first In the more serious cases the trunk muscles also atrophy At first the patient is able to move about with the aid of a cane but later he becomes confined to bed During convalescence his gait may become spastic The muscles give the electrical reactions of de generation The muscular reflexes are diminished and later lost When first examined the patellar reflex may be found impaired or even lost It may remain absent long after apparent recovery indicating that the damage to the nervous system is repaired very slowly

Combined with the muscular degeneration are the sensory changes usually consisting of areas of anesthesia or various paraesthesias Like the motor dis turbances they appear first on the lower leg particularly over the anterior surfaces The anesthesia is at first partial so that the prick of a pin may be felt only as a touch but on the other hand the sensation may be delayed Later the anesthesia is complete so that a patient may be prodded until the blood runs without feeling it Perception of heat cold and pain is diminished in the areas supplied by the degenerated nerves The paraesthesias consist of sensations of heat prickly sensations formication and itching

In other cases the atrophy of the muscles is less marked or appears so be cause it is masked by the extensive edema This edema commences in the feet and legs and may be confined to these parts but often ascends the thighs and gradually extends over the body At this time there is usually some hydroperi cardium and hydrothorax The hydropericardium which is the most frequent effusion is hard to diagnose by physical signs because of the hypertrophy of the heart which is present There may be a large amount of fluid in the thorax which may cause much respiratory embarrassment It may be detected by the usual physical signs

Epigastric distress precordial pain palpitation and dyspnea may at times be the most striking symptoms pointing to the incompetency of the heart muscle Such symptoms may be mild and continuous but are likely to occur in sudden paroxysms Thus a patient who has previously not been considered seriously ill may be suddenly seized by a horrible boring precordial pain He gasps for breath and his face becomes cyanosed On examination the heart is irregular the pulse small and thready and a venous pulse appears Death often follows this sudden dilatation a complication that is particularly frequent in the wet type of beriberi These deaths should now be avoided

A hypertrophied heart in an endemic area of beriberi should arouse im mediate suspicion An electrocardiogram should show changes in the T waves and prolongation of the electrical systole (Q–T) If such a case is promptly treated with thiamin the cardiac weakness is promptly relieved In the absence of cardiac accident the patient may linger in the hospital for weeks or months

until as a result of adequate diet the symptoms of the peripheral neuritis improve the atrophied muscles recover their tone and strength and the patient walks and exercises with increasing ease During this time almost certainly as the result of some change of diet or after the administration of thiamin one of the swollen dropsical cases suddenly passes greatly increased quantities of urine The edema subsides rapidly and perhaps then shrunken muscles stand revealed The apparently robust limbs have disguised the muscular wasting and a case of wet beriberi has been transformed into a case of dry beriberi

Aphonia is a symptom that requires special mention for it occurs with some frequency in adult cases and more often in infantile beriberi The speaking voice is lost and the patient can only whisper This symptom is attributed to the paralysis of the muscles of the larynx following degeneration of the recurrent laryngeal nerves It was described in the first European account of beriberi by Bontius in 164-

Beriberi is not a febrile disease but it may be complicated by infection There is reason to believe that those suffering from deficiency diseases may on this account be more than usually susceptible to infection Malaria dysentery and tuberculosis are common in the countries where beriberi is endemic

There are no characteristic changes in the blood in beriberi A moderate anemia is to be expected but usually neither the red cells nor the hemoglobin are seriously reduced The leukocyte count will be normal in the absence of infection but there is apt to be a relative lymphocytosis with a slight shift to the left in the polymorphonuclear neutrophils This is a common finding in the tropics especially in debilitated persons

The urine is usually normal in amount and constituents The exceptions to this rule have some significance When edema appears and as it progresses the quantity of urine is greatly diminished Mothers with infants suffering from infantile beriberi notice this symptom particularly One or two diapers a day are all that are required Albumin casts and even blood may be found This generally indicates severe right sided cardiac embarrassment with venous back pressure and severe congestion of the kidneys Since nephritis is no part of the picture of beriberi and has nothing to do with the formation of the edema such urine findings signify that acute cardiac failure is not far off Prompt administration of thiamin is indicated

DIAGNOSIS

Individual cases particularly among Europeans or Americans may present considerable difficulty It is now believed that alcoholic neuritis is also caused by a deficiency of thiamin in the diet since alcoholics not only fail to follow a proper diet but a large part of the calories is furnished by the alcohol which is absolutely deficient in all vitamins Several observers have said that they had relieved alcoholic neuritis with thiamin treatment

The diagnosis of beriberi is usually simple among Orientals especially in the presence of a definite outbreak of the disease There is no disease except beriberi that presents at the same time the three symptom complexes of peripheral neuritis cardiac hypertrophy with weakness and edema with serous effusions

In the presence of these syndromes the peripheral neuritis caused by alcohol arsenic lead and other intoxicants can be excluded Oriental races use little alcohol they are much more apt to be opium users

The history of a deficient diet usually can be obtained if the clinician is familiar with the articles of diet that are deficient in vitamins and that produce beriberi In Orientals the fault is almost the too exclusive use of decorticated white rice and in jails and asylums in Europe and America including Labrador and Newfoundland it is the too exclusive use of white bread

True heart disease and nephritis must also be excluded There are no valvular lesions in beriberi although it is always possible that a case of true valvular heart disease could also develop beriberi In any case the presence of signs of peripheral neuritis should lead to an investigation of the diet Although albumen and casts may be found in beriberi following congestion of the kidneys this is by no means the rule The urine is usually normal There is no nitrogen retention and in fact in Orientals who eat almost no meat urea nitrogen and creatinine are low as compared with normal levels for Americans In beriberi the blood pressure falls instead of increasing as in nephritis

The effect of epinephrine in beriberi in causing a fall in diastolic blood pressure was pointed out by Alsmeer The diastolic pressure is determined first of all then epinephrine is administered hypodermatically in a dose of 1 mg and the diastolic pressure observed every five minutes thereafter The epinephrine will bring the diastolic pressure down to zero in a case of beriberi and there will be an ausculatory murmur that will persist even on complete relaxation of the pressure on the artery as long as the patient is under the influence of epinephrine There is already a considerable arteriolar dilatation and a rapid blood flow in cases of beriberi with cardiac changes The epinephrine stimulates the heart but it also dilates the blood vessels yet further A pulse is therefore produced somewhat like the Corrigan pulse in aortic insufficiency a pulse of considerable volume which rapidly recedes

PROGNOSIS

The mortality in some reported outbreaks has been very high but the average may be placed at from 3 to 5 per cent These deaths are all caused by acute cardiac dilatation and it has already been pointed out that proper treatment should reduce this mortality practically to zero

In those cases in which the peripheral neuritis is marked with great muscular weakness and atrophy recovery is necessarily slow and is not to be expected immediately even with thiamin treatment and an adequate diet The damage to the nervous system is extensive and has progressed for months Also convalescence is generally a matter of weeks or months and the reflexes may still be abnormal even after the patient is able to walk and appears normal

TREATMENT

Any patient with cardiac hypertrophy or other cardiac condition should be kept in bed Venesection was first proposed by Anderson in 1887 and has been used subsequently with excellent results When cardiac dilatation has already

taken place and the patient is obviously in grave danger of cardiac failure the prompt abstraction of blood relieves the overburdened right side of the heart But this is only an emergency measure Extensive pleural effusions should be relieved by tapping But aside from such emergencies the treatment should consist of thiamin therapy From 20 to 50 mg of thiamin chloride should be given intravenously each day until the heart and circulation have returned to normal With these doses improvement begins at once The heart should be normal and the edema should be dissipated in the course of a few days Intravenous injection is far more effective than thiamin by mouth Thiamin administered intravenously will also relieve many of the symptoms caused by the peripheral neuritis If the peripheral neuritis is mild it may be relieved completely but advanced cases cannot recover with the use of thiamin alone

After all that can be accomplished by thiamin therapy has been achieved further treatment is purely dietetic A high vitamin diet should be selected Rice should be limited in amount and should be undermilled Meat eggs milk and leafy vegetables should be used freely There is good evidence that at least part of the nerve degeneration may be due to deficiency in vitamins A and B complex A complete diet is therefore not only good sense but may be required for complete recovery

PROPHYLAXIS

Theoretically prophylaxis is extremely simple Use only undermilled rice and eat sufficient eggs meat and vegetables Practically this cannot be done Orientals like good food as much as anyone else With the exception of a few cases of beriberi originating from food fads beriberi is a disease of poverty The Oriental eats so much rice because he cannot afford other foods He eats rice just as we eat bread and demands it just as we demand bread He also demands white rice just as we demand white bread and both are about equally deficient in vitamins

When undermilled rice is issued each lot of rice purchased must be examined by some central authority to be sure that enough of the external layers of the grain is intact If the rice is placed in a dish and covered with Gram s iodine solution the exposed starch turns black on contact with the iodine If the rice has been completely decorticated the entire grain turns black This is the rice that will produce beriberi On the other hand in an undermilled rice the starch will be protected from this action by the external layers of the grain and will be only partly stained When whole rice that has been husked but not milled is tested the starch will not be stained at all With a little experience examiners can select with certainty rice containing sufficient of the germ and external layers to prevent beriberi by this method

Rice may also be examined chemically for the same purpose In addition to vitamin B_1 most of the phosphorus and fat is contained in the external layers and is removed by milling A standard of 0 4 per cent phosphorus pentoxide was originally proposed by Fraser and Stanton in 1911 They believed that no rice containing that amount of phosphorus would produce beriberi It was later found that in a few instances beriberi occurred from rices complying with

this standard and consequently the standard was raised to 0.5 per cent phosphorus pentoxide In 1920 Vedder and Feliciano published end results of a study of 200 different rices The chemical index proposed by this study was 1 77 per cent of phosphorus pentoxide plus fat or any rice having not less than 0 62 per cent phosphorus pentoxide No rice possessing these qualifications produced polyneuritis in pigeons

INFANTILE BERIBERI

Infantile beriberi is true beriberi affecting infants who are breast fed and whose mothers suffer from manifest or latent beriberi Infantile beriberi may appear soon after birth and 80 per cent of the cases occur during the first three months of life It is rare after the fifth month Like adult beriberi the disease is caused by the same vitamin deficiencies in the diet which in these cases is the milk of a mother who is unable to excrete the vitamins in the milk It is characterized clinically by a mild peripheral neuritis generalized edema and serous effusions and especially by cardiac hypertrophy and acute dilatation that result in sudden death

HISTORICAL NOTE

The disease was first described by Hirota in Japan in 1898 It was recognized in the Philippines by Guerrero and Quintos by Albert and by Andrews in his postmortem findings and experimental work A large part of the infantile mortality in the Philippines is caused by this disease and consequently the mortality is very high among breast fed babies

ETIOLOGY

Only breast fed babies suffer from the disease Often a mother loses several children in this way and she saves others by artificial feeding Andrews showed that puppies developed beriberi when fed exclusively on the milk of women whose children had died of infantile beriberi

It was suggested that the disease was caused by a toxin secreted in the mother s milk However Chamberlain and Vedder in 1912 succeeded in curing a number of cases of infantile beriberi by administering to the infants the extract of rice polish which had been shown to prevent polyneuritis in fowls that had been fed exclusively on polished rice The infants so treated recovered in several days So successful was this extract that it was prepared by the Bureau of Science in Manila for free distribution and Wells 19 1 reported that 47,530 bottles of 50 cc each had been issued In 1938 Hawes obtained similar results by treating the infants with pure crystalline thiamin and concluded that infantile beriberi was probably the purest form of B_1 deficiency

PATHOLOGY

The gross pathology is identical with that of a case of wet beriberi At postmortem the right side of the heart is seen to be greatly hypertrophied and dilated and there is general anasarca

SYMPTOMATOLOGY

While chronic dry cases were described by Guerrero and Quintos the only cases that come to postmortem examination are of the acute wet type The only warning is that the urinary secretion is markedly diminished so that very few diapers are used When this happens in a breast fed baby under three months it should be treated at once In the absence of specific therapy edema increases and the child is suddenly seized with an acute cardiac crisis. The child cries constantly straightens out its body and becomes quite rigid The face becomes cyanosed and the pulse is small rapid and irregular The heart is enlarged and beats rapidly and irregularly The second pulmonic sound is accentuated and the blood pressure is very low In this condition the child may die in a few minutes The death is so sudden that it is rare for the physician to see these cases prior to death In the rarer dry cases the child has a waxy appearance and shows great weakness of the limbs and especially aphonia or loss of the normal voice

PROGNOSIS

The disease is fatal if the infant continues to be breast fed by its mother and is not given treatment Feeding by a healthy wet nurse is the best procedure since the mortality of afflicted infants artificially fed is also high Immediate intravenous treatment with thiamin will relieve all symptoms promptly but they will recur if the child continues to be fed milk from its mother

PROPHYLAXIS

If the mothers are properly fed during pregnancy and lactation the disease will not occur When it is known that the diet of the mother is deficient a prophylactic dose of rice polish extract may be given the child daily until it is six months of age Under these circumstances the mother can continue to nurse it Otherwise the alternative is to use artificial feeding or a wet nurse whose children do not die

EPIDEMIC DROPSY

Epidemic dropsy is a nutritional disease that occurs in sudden outbreaks among rice eaters Clinically it is characterized by marked generalized edema and cardiac enlargement and to this extent it resembles wet beriberi But fever is common and there is sometimes an erythematous eruption on the extremities

HISTORICAL NOTE

In 1876 during a famine in India a disease appeared whose principal symptom was dropsy It was described as beriberi The term epidemic dropsy was first used by McCleod who described a similar disease that appeared in Calcutta from 1877 to 1880 Since that time epidemic dropsy has occurred in various parts of India Again in 1908 Pearce stated that epidemic dropsy was

beriberi and in 1912 Greig after considerable epidemiologic survey concluded that epidemic dropsy was a deficiency disease Megaw in 1927 believed that while closely related to beriberi epidemic dropsy had certain features that differed from it

ETIOLOGY

Greig not only found that the diet in all the cases was deficient but also that epidemics commenced and declined with the rise and fall of food grains As the price of rice rose the natives could not purchase the supplementary and protective articles of diet Then the disease appeared Greig found 52 cases of scurvy among his 630 cases of epidemic dropsy

While in India the disease occurs only among rice eaters an edema disease was described by Mann in 19 4 among prisoners in Haiti These prisoners were fed on cornmeal and lard but no rice and they presented many features of epidemic dropsy including a very large number of deaths This was also a purely nutritional disease because it promptly disappeared when the diet improved

From 1938 to 1940 several Indian investigators have incriminated the mustard oil that is very generally used in India for cooking The mustard oil itself is harmless but certain samples have been contaminated with the seed of *Argemona mexicana* which it is believed is highly toxic One observation indicated that administration of this argemone oil to guinea pigs and white mice gave rise to symptoms of epidemic dropsy It should be noted that it is very easy to kill guinea pigs by administration of any fat including harmless butter In addition these observers described advanced fatty degeneration of the liver and acute glomerulotubular hemorrhagic nephritis conditions which are no part of epidemic dropsy

The entire question is still open and the probability is that it is a deficiency disease very like beriberi but with certain differences Possibly these differences may be due to the toxic effects of argemone oil

PATHOLOGY

Only a few autopsies are recorded Death is caused by cardiac hypertrophy with dilatation of the right side of the heart Edema is present in the subcutaneous tissues particularly in the legs but sometim s over the whole body Serous effusions are common and the lungs are edematous The stomach and duodenum are congested and present small ecchymoses The liver spleen and kidneys are much congested These lesions are the usual pathologic findings in cases of wet beriberi with acute cardiac failure But in addition to this a dilated and engorged capillary angiomatous condition has been described which by some Indian writers has been called sarcoids These lesions vary from pin point size to one third of an inch in diameter The significant statement was made by one observer that microscopically no signs of inflammatory reaction are seen

SYMPTOMATOLOGY

Epidemic dropsy presents all the symptomatology of wet beriberi but it differs in that (1) fever is common (2) the angiomatous condition just described is common and (3) glaucoma occurs not infrequently

Epidemic dropsy is often described as beginning with fever the temperature ranging from 37 to 40 C (99 to 104 F) This fever lasts for variable periods of time and is often associated with some diarrhea Edema commences soon after That the fever is not an essential part of the disease is indicated by the fact that Greig found fever in only 3°° of 620 cases In a country where malaria is the commonest single disease and where other infections are frequent fever in a considerable number of cases of any disease is to be expected Moreover we now know that the demands of the body for thiamin are greatly increased by fever What could be more likely than that a patient suffering from fever develops acute thiamin shortage and that the beriberi heart and dropsy *are the results? It has been noted that as in beriberi* digitalis strophanthin and other drugs are of no effect Unfortunately the administration of thiamin appears never to have been applied

The description of the lesions in the skin leaves something to be desired The sarcoids has been applied only by Indian observers who are wedded to the argemone oil theory Previous European observers described these lesions as petechiae or small subcutaneous hemorrhages and a mottling over the edematous parts Such a condition might be mild scurvy Greig found that of his 630 cases 180 had mild symptoms of scurvy and 5° or 8 per cent suffered from manifest scurvy with characteristic stomatitis and bleeding from the gums and hemorrhages from the bowel While it cannot be asserted that the skin manifestation of epidemic dropsy is a manifestation of scurvy that explanation appears to be the most probable

There is no satisfactory explanation for more glaucoma in epidemic dropsy than in wet beriberi It has been claimed that it responds promptly to the administration of the hormone cortin in which case it may be merely a part of the greatly disturbed water metabolism in epidemic dropsy

Apparently the only characteristic and constant symptom is the dropsy This occurs early and may be the first symptom It appears regularly in the feet and legs but often progresses to the trunk and upper extremities In the same 630 cases edema occurred in the feet alone in 8 cases in feet and legs in 442 cases and in the entire body in 129 cases This edema lasted from three to six months The cardiac symptoms are dyspnea which may be severe palpitation and precordial pain With cardiac failure cyanosis venous pulsation increased pulmonic second sound and falling blood pressure are found From ° to 5 per cent of the patients die from this acute dilatation of the right side of *the heart*

Gastro intestinal symptoms are common and include vomiting diarrhea and loss of appetite At least a third of the patients present such symptoms which in view of the congestion of the abdominal organs is to be expected

The symptoms of peripheral neuritis may be lacking and are generally mild when they do occur Tenderness of the muscle of the calves was found in 30 per cent of the cases and muscular weaknes in about 24 per cent

TREATMENT

The only known treatment is a full and generous diet which is difficult to secure since most of these patients will eat no meat The administration of thiamin should be tried and a most interesting experiment would be to try the effect of ascorbic acid on the skin lesions

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CHAPTER 11

PELLAGRA

EDWARD B VEDDER

PELLAGRA IS A DISEASE OF FAULTY METABOLISM USUALLY found among maize eaters whose diets are deficient in niacin (nicotinic acid) and other vitamins Clinically it is characterized by symmetrical erythematous lesions that develop into a pigmented exfoliative dermatitis by alimentary disturbances including stomatitis and glossitis gastro-enteritis with diarrhea and proctitis and by nervous manifestations that often lead to dementia

HISTORICAL NOTE

In 172_5 Casal recognized in Spain a disease differing from any known to the physicians at that time which he called ascorbutic leprosy We regard this as the first description of the disease now known as pellagra It was also known to the Spaniards as mal de rosa It was next reported from Milan by Frapolli in 1771 and was a serious problem in Italy for at least a century During this time it was studied by many physicians and given its present name which means rough skin

ETIOLOGY

Ideas concerning the cause of pellagra went through about the same evolution here as in Italy the condition was first attributed to maize then to spoiled maize and later to some unknown infection The Robert M Thompson Pellagra Commission consisting of Siler Garrison and MacNeal adhered to the belief that the disease was infectious but they found that individuals who consumed sufficient quantities of milk eggs or meat were protected Joseph Goldberger of the United States Public Health Service commenced observations in 1914 He and his collaborators were convinced that pellagra was a deficiency disease The pellagra producing diet when given to dogs produced a condition known as blacktongue This disease has been generally considered as the analogue of pellagra in man Blacktongue could be cured with yeast and it was found subsequently that pellagra in human beings could also be cured with yeast Goldberger described the vitamin required by pellagrins and by blacktongue dogs as the pellagra preventing (P P) factor This work

taken as a whole was the greatest single advance in the knowledge of pellagra in the history of the disease

Minot and Murphy discovered in 19 4 that liver and liver extracts could cure pernicious anemia It was found subsequently that these substances were curative in sprue There are some obvious clinical resemblances between the symptoms of pernicious anemia sprue and pellagra They all have sore mouth at least two have diarrhea while pernicious anemia sometimes has diarrhea The addition of liver and liver extracts to pellagra treatment soon followed. Boggs and Padgett in 1928 reported a series of cases of pellagra in which liver was used in the diet and found it effective in relieving the symptoms In the few cases in which liver extract was used it was fully effective Other observers soon corroborated these results and later it was found that liver extract would also cure blacktongue in dogs

In 1937 Elvehjem and his collaborators stated that the effective agent in the cure of blacktongue was nicotinic acid and suggested its use in treatment of human pellagra Since that time many investigators including Spies and his collaborators have treated pellagrins with nicotinic acid (niacin) or with nicotinic acid amide (niacin amide) It has been found that all the classic symptoms of pellagra including even the mental symptoms are promptly relieved by this treatment when administered either by mouth or parenterally However shortly thereafter it was noted that pellagrous patients treated in this way developed classic symptoms of riboflavin deficiency thiamin deficiency or both but that these symptoms also disappeared after appropriate vitamin therapy Vitamin B_6 and pantothenic acid were useful in the treatment of certain other symptoms

It has accordingly been demonstrated that pellagra is a complex deficiency chiefly of niacin but to a greater or less extent of many of the fractions of the B complex However the classic symptoms of the disease are all responsive to the administration of niacin or of niacin amide It is interesting to note that milk eggs and meat which the Robert M Thompson Pellagra Commission found afforded protection are all reasonably high in niacin content

While exposure to moderate sunlight has no effect upon normal persons or at most causes tanning there is good experimental evidence to indicate that those individuals subsisting on a pellagra producing diet develop the typical erythema of pellagra when exposed to sunshine that produces no effect on normal people It has also been noted that the skin lesions of pellagra appear regularly during the months of greatest sunlight and improve as the sunlight diminishes Since sunlight affects the exposed portions of the body symmetrically this fact may explain the remarkable bilateral symmetry of the skin lesions When pellagrins have recovered after the administration of niacin sunshine no longer produces pellagrous lesions so that on long exposure they become tanned like normal individuals One of the Italian designations for pellagra is mal de sole Other investigators deny the effect of the sun and point out that the eruption often occurs on completely covered parts of the body

EPIDEMIOLOGY

Usually it will be found that the bulk of the diet is composed of cornmeal and white wheat flour both of which are very low in niacin content while higher priced protective foods such as meats milk and eggs are conspicuous by their absence This is partly due to ignorance but chiefly to poverty

In female patients the number of children born and nursed is important Although pellagra occurs in infancy having been reported as early as the seventh month its incidence in childhood is the same in boys and girls But after the age of sixteen and until the age of forty five to sixty years females show a much higher incidence of pellagra than males This is undoubtedly due to the influence of child bearing which greatly increases the female metabolism and need for niacin and other vitamins and foods After the age of fifty males and females are again approximately equal as far as the incidence of pellagra is concerned

Of the 1 180 pellagrins studied by the Robert M Thompson Pellagra Commission 1 027 were white and 153 colored a ratio of 6 7 1 According to the census figures of 1910 pellagra morbidity of Negroes was about one third the morbidity rate for pellagra of the entire population They are certainly no more resistant to the disease for of the 1 0 7 white pellagrins 123 or 12 per cent died while of 153 Negro pellagrins 64 or 41 8 per cent died Searcy's original report showed a high death rate of 64 per cent for Negroes in an insane asylum Under most circumstances Negroes have less pellagra than whites As they have less need to keep up appearances they spend a higher percentage of their income on food

Geographical Distribution Pellagra has been noted quite commonly in Italy Spain Portugal the Balkan states Greece and Turkey It has been frequent in Lower Egypt but rare in Upper Egypt Pellagra occurs also in India the Straits Settlements China Japan and West Indies In the United States it has been prevalent especially in the southeastern states

PATHOLOGY

The skin lesion commences with erythema which is followed by pigmentation and a true exfoliative dermatitis These lesions are most frequent on the backs of the hands and forearms on the feet and legs and on the face that is on the most exposed parts of the body On the neck the eruption is known as Casal's collar But lesions of the scrotum and the vulva are not rare

On postmortem examination emaciation is found to be marked and all organs including the heart are smaller than normal The most constant findings are in the *gastro intestinal tract* which is greatly inflamed and frequently ulcerated This inflammation begins with marked stomatitis and glossitis and continues through the small intestine into the colon including the rectum But these are the cases that die While the lesion in the average case may be of the same general nature it must not be supposed that the intestinal and colonic inflammation is so acute or so severe

There are characteristic lesions in the *nervous system* In the cord the tracts of Gall and Burdach show degeneration and proliferation The tracts are pale compared with the rest of the cord Occasionally degenerate roots entering in the lumbar region can be traced up to the dorsal region The degenerated areas in the posterior columns when stained by the Marchi method look like small spots of ink spattered all over the area The direct pyramidal tract also shows more or less degeneration and scattered areas from which the nerve fibers have disappeared Occasionally swollen axis cylinders are found

In the gray matter there is pigmentation of the cells of both anterior and posterior horns The fibrils appear contracted and the cells smaller The cells of the posterior horns appear to be degenerated from the cervical region downward the cells in Clarke s column are especially affected In the anterior horns in the lumbar region the cell bodies are swollen and the nucleus is displaced to the periphery as a result of intense chromatolysis

In the brain leptomeningitis cerebral atrophy and increased ventricular fluid may be found There is an anatomic basis for the mental changes although these cannot be irreversible since they clear up after niacin therapy Again it must be remembered that these changes were found in patients who died of pellagra

SYMPTOMATOLOGY

The typical triad of dermatitis diarrhea and dementia is readily recognized but many early cases have no dermatitis and were formerly called pellagra *sine* pellagra or incipient pellagra It is possible to recognize several types of the disease

Mild cases presenting sore mouth alternating diarrhea and constipation indigestion and neuroses In this the clinical diagnosis is difficult

Cases of moderate severity in which all the symptoms are more pronounced and in which the dermatitis appears In earlier years these were not diagnosed until dermatitis was present These patients improve in the fall and relapse the next spring

Severe cases in which the mouth symptoms are severe the diarrhea intractable the dermatitis pronounced and extensive with definite mental deterioration Emaciation is marked fever develops and in former years the patient died

Although dermatitis may be a very early symptom in mild cases and may readily lead to a diagnosis of pellagra such individuals are not always included in this category Sore mouth and tongue are present in most of these patients but unfortunately these symptoms are not in themselves diagnostic since they are present in pernicious anemia sprue and simple achlorhydria The early gastro intestinal symptoms are not typical either Everyone has occasional indigestion and diarrhea The nervous symptoms are vague and may be labelled psychasthenia or neurasthenia

The earliest and most constant symptom of the disease is loss of strength and a feeling of weakness often referred to the legs The patient has increasing

difficulty in walking Concomitantly there is some loss of weight though this may not be noticed

Gastro intestinal symptoms are evident usually before the appearance of the skin lesions The patient complains of a scalding sensation in the mouth increased by highly seasoned foods or hot drinks In some cases this burning sensation may extend to the esophagus or to the entire gastro intestinal tract. The tongue is found to be red when it is examined At first confined to the tip and edges later the *entire tongue loses the superficial epithelium* and is acutely inflamed The mucosa of the mouth may also be reddened The gums are tender and bleed readily Salivation often occurs in this condition and may be intense with continuous dribbling These symptoms strongly resemble sprue one name of which is psilosis In this condition it is difficult for the patient to eat at all

Loss of appetite is one of the most common complaints When the pellagrin eats he does so sparingly because he is quickly satiated and also because the ingestion of food is followed by a feeling of distention gas and burning *Nausea is common sometimes followed by vomiting These symptoms* are often regarded as indigestion and the variety of food is further restricted as the patient believes one article after another disagrees with him

In early and mild cases the stools are usually normal Commencing with constipation alternating with diarrhea a chronic diarrhea is later established with stools varying from three to thirty a day In severe cases the stools may be dysenteric with mucus and blood but usually they are liquid and profuse Burning in the rectum causes a constant desire to go to stool Proctoscopic examination will reveal a general inflammation of the mucous membrane *sometimes with ulcerations*

It follows both as the result of the restricted food intake and of the diarrhea that emaciation is rapid Unless these symptoms can be relieved death is inevitable Fortunately even such cases of pellagra can be promptly relieved by adequate amounts of niacin and at the present time patients are seldom permitted to progress so far without treatment

Mental and nervous symptoms Insomnia is a frequent symptom of nervous disorder and may be related to mental derangement Insomnia combined with fear results in marked depression and may indicate that insanity is commencing Without treatment the mental changes finally end in a dementia which requires institutional care

Sensory disturbances take place early Burning of the feet is common before the eruption appears and this symptom is also an early sign of thiamin deficiency The sensation of formication is common also pains in the extremities particularly *the legs and may be the result of peripheral* neuritis While knee jerks are often exaggerated they may be decreased or absent Cord changes with abnormal gait are a late manifestation and like the changes caused by pernicious anemia do not always disappear after proper therapy It is noteworthy that the tongue intestinal skin and mental symptoms dis

appear after the administration of niacin but that many patients are left with a definite polyneuritis which clears up with thiamin treatment

In a considerable proportion of the cases the skin eruption either does not appear or is so mild as to escape notice—pellagra *sine* pellagra Experimentally it has been found that the eruption first appears after three to five months on the deficient diet

Skin manifestations The first manifestation of skin lesions looks like sunburn of the hands and face but this sunburn is sharply circumscribed and is symmetrical It increases in intensity and area with thickening and pigmentation of the skin The latter peels off and the skin is rough to the touch hence the Italian name pelle agra In some cases the eruption is of a deeper color with bleb formation and is described as the wet type

This characteristic symmetrical lesion may affect any part of the body but it is commoner on exposed portions of the body as the backs of the hands or on the arms up to the elbows when the sleeves are rolled back the upper surface of the feet the neck and the face Less frequent sites are the elbows knees and genitalia both male and female More rarely the skin of the back the abdominal surface and the thighs may be affected A relatively uncommon type encircling the neck is known as Casal s collar After desquamation is completed a reddened shining skin is left which appears thinner than normal especially after several attacks

In the United States this eruption appears regularly from April to July and usually clears up by early fall that is by September or October This period is probably related to the periodic deficiency in diet which is most acute in the winter months while in the summer garden vegetables and fruits are available and the deficiency is relieved Many of these pellagrous patients have repeated eruptions every spring The lesions often occur without exposure to the sun yet most observers believe that sunshine and even heat from a stove assist in causing the eruption

Laboratory studies In mild cases the blood is normal but in moderate and severe cases anemia is constant The anemia is usually normocytic and hypochromic This may be caused by deficiencies without which the protein constituent of hemoglobin cannot be formed but it is more probably a simple iron deficiency Investigation of the diets of pellagrins shows that they eat very little or no meat A few cases of pernicious anemia have been described but because of its rarity this is probably a concomitant condition The usual erythrocyte count will range from 3 000 000 to 3 500 000 per cmm with hemoglobin from 50 to 70 per cent Leukopenia with some lymphocytosis is the rule

Achlorhydria occurs in a high percentage of cases Of 3[illegible]4 cases on record as having received test meals hydrochloric acid was found in only 96 and achlorhydria in [illegible]7 cases but this condition was not always permanent A considerable percentage of normal individuals of forty five years or over have achlorhydria Lacking information regarding the ages of the pellagrins examined we can say only that achlorhydria is common in the disease

There is nothing characteristic about the stools At present two tests are used to identify early cases of pellagra one clinical and the other therapeutic i e the administration of niacin The clinical test was devised by Spies and his collaborators and is the detection of ether soluble red pigments in the urine *which were at first thought to be due to porphyrinuria It is now known* that this is not the case Neither is the test specific since it may be noted after roentgen ray sickness disorders of the intestinal tract and possibly other conditions However it is found constantly in these early cases of pellagra and i a great diagnostic aid

The test is performed as follows To 10 cc of urine in a separatory funnel add about 0 2 cc of glacial acetic acid to make a pH of 4 Then add 15 to 20 cc of ether and shake After separation the lower aqueous layer is drained off and the ether is washed with 10 cc of distilled water To the washed ether extract add 3 cc. of 25 per cent hydrochloric acid The mixture is shaken and then transferred to a test tube When positive specimens of urine are used a pink to purple color develops on addition of the hydrochloric acid While these patients may have no diagnostic lesions of pellagra this test becomes negative after treatment with niacin or its amide There are also urinary tests for the amount of excreted thiamin and pyridoxine These tests are rather complicated and those interested in them should consult the original literature

In the spinal fluid the cell count is not increased

COMPLICATIONS

In a disease that lasts as long as pellagra there is always the possibility of association with other diseases The occasional occurrence of pernicious anemia has been mentioned Many cases especially in Negroes are associated with syphilis tuberculosis or hookworm infestation Dysentery either bacillary or amebic finds an excellent soil in the debilitated pellagrin with an already inflamed intestine and rectum

DIAGNOSIS

Although the diagnosis of a fully developed case of pellagra can hardly be missed the diagnosis of early cases in the absence of eruption may be attended with great difficulty Many of these resemble cases of sprue but the characteristic sprue stool is missing nor is there such a tendency to macrocytic anemia A test for the ether soluble pigments in the urine may resolve the difficulty Ordinary sunburn dermatitis venenata and eczema may be mistaken for the eruption The sharp delineation of the lesion the pigmentation and roughening of the skin as well as the manner of development and tendency to recur on successive years are distinguishing points in favor of pellagra

PROGNOSIS

Formerly the death rate in cases admitted to the hospitals ranged from 30 to 60 per cent The cases studied by the Thompson Pellagra Commission had

a mortality of 15 8 per cent but they were all moderately severe cases Taking all pellagra cases as they occur we may expect an average mortality of 3 per cent which seems rather low However considering the large number of cases this results in a very heavy total mortality Actually at the present day there should be no mortality at all Spies and his collaborators using the modern vitamin treatment lost none of their patients The possibilities of a recurrence after such treatment are almost certain unless the proper permanent changes are made in the diet

TREATMENT

Both yeast and liver extract have been found effective because of their niacin content The administration of niacin or preferably niacin amide results in the alleviation of the specific lesions of pellagra in the course of a few days The therapeutic dose is 300 to 500 mg by mouth daily for five to seven days The administration of ten doses of 50 mg each at hourly intervals is more effective than a single large dose and far more comfortable Absorption of niacin in doses of 100 mg and up may be followed in less than half an hour by flushing and a sensation of burning heat over the face ears and neck This flushing is due to peripheral vasodilatation The sensation is quite harmless and passes away in an hour Niacin amide does not produce this reaction and is therefore to be preferred but it is more expensive

After the symptoms have been relieved a daily dose of 100 mg may be maintained for a few days longer to produce complete saturation With this dosage the mucous membrane lesions the skin eruption and even the mental symptoms clear up as though by magic But such patients are often left with some peripheral neuritis which yields to thiamin administration Certain forms of glossitis and cheilosis are relieved by riboflavin administraton There is some evidence that these patients are also relieved by the administration of pyridoxine and pantothenic acid

Since pellagra is a complicated deficiency in spite of the fact that most of the specific symptoms are caused by deficiency in niacin the only permanent cure for such cases is a good diet and this must be outlined for every case for otherwise the disease will surely recur the next year The essentials for a proper diet are 3 000 to 4 000 calories daily and milk eggs lean meats liver and fresh green leafy vegetables should be included The diet of pellagrins is notably deficient in milk eggs meat and green vegetables during the winter During the summer months they eat a good supply of leafy vegetables such as beet greens dandelions and turnip tops as well as string beans and other vegetables and their improvement in the fall may be ascribed to this

Unfortunately meat liver eggs milk and fresh greens during the winter are among the most expensive of foods and pellagra is a disease chiefly of those who cannot afford these foods This expense may be largely overcome by keeping chickens or a cow or having a kitchen garden This is also difficult for those who work all day in a factory but when they have been taught that the alternative is pellagra unless adequate quantities of these foods are con

sumed they may be willing to make the effort Spies Grant and Grant in 1941 announced that a mixture containing 25 per cent brewers yeast powder incorporated in 67 per cent peanut butter and 8 per cent peanut oil is an inexpensive and palatable food mixture that tends to prevent pellagra beriberi and riboflavin deficiency Two ounces or more of this is used daily as a supplement to the food It makes a good spread for sandwiches

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CHAPTER LII

SPRUE

EDWARD B VEDDER

SPRUE IS CAUSED BY FUNCTIONALLY IMPAIRED INTESTINAL absorption which results in the deprivation first of fat and later of vitamins and other food constituents Untreated sprue is steadily progressive and is characterized clinically by gastro intestinal symptoms including a sore mouth and tongue and a chronic diarrheal condition by great emaciation and by macrocytic anemia indistinguishable by blood studies from pernicious anemia

HISTORICAL NOTE

In 1759 William Hillary described a chronic type of diarrhea associated with sore tongue pallor and emaciation which he had observed in Barbadoes A century later in 1864 Julien described Cochin China diarrhea a similar disease and stated that it was a specific condition that differed from dysentery and the ordinary diarrheas In 1880 Manson in Amoy and Van der Burg in Java reported more fully the clinical features of the disease which was named sprue Since that time sprue has been established as a disease entity

ETIOLOGY

Sprue is pre eminently a disease affecting European races in warm moist countries but it may develop in cold climates in individuals who have lived in the tropics

More recently non tropical sprue has been reported In 1939 Snell described 3 such cases in persons who had never left temperate climates and concluded that there was no essential difference between tropical and non tropical sprue This conclusion is not accepted by all authorities

While it remains possible that sprue may be initiated by a *deficient diet* this is not the usual cause because the condition has often appeared in individuals known to have eaten diets adequate in all particulars Moreover although sprue may occur in either man or woman either husband or wife may develop the disease while eating the same diet It is seldom found in both

In 1923 Scott suggested that *parathyroid and calcium* deficiency caused sprue and he treated cases with calcium lactate and parathyroid We know now that calcium deficiency is a result and not the cause of this disease Cal

cium is excreted by the intestine in large amounts with the result that muscular cramps or a mild form of tetany is a frequent symptom

In 1926 Minot and Murphy instituted the liver treatment for pernicious anemia and this treatment was soon thereafter applied to sprue Cases of sprue were cured by liver extract especially when given parenterally When given in large amounts the extract not only relieves the anemia but since complete recovery eventually takes place so that the extract is no longer required it must be assumed that there is no permanent lesion of the intestine and that the failure of absorption is due to a functional intestinal change

PATHOLOGY

Fatal cases of sprue were formerly common At necropsy the tissues are found to be dry and devoid of fat The muscles are wasted and all the internal organs particularly the heart liver and spleen are atrophied and much smaller than normal Similar changes are found in actual starvation In addition there is megaloblastic hypertrophy of the red marrow

With regard to the intestines the organ chiefly affected thinning of the mucosa with disappearance of the valvulae conniventes as well as thinning of the muscular coats has been described But Mackie and Fairley in autopsies performed immediately after death found the intestines to be morphologically normal Certainly there are no irreversible changes since moribund cases that formerly would have died are now saved and return to accustomed health as a result of the proper use of liver extract

Mackie and Mills have studied the intestines in sprue roentgenologically They find that in the duodenum and jejunum the mucosal markings are coarser than normal There is a striking variation in the contour and size of the lumen and abnormal collections of gas may be present The normal motor activity is disturbed frequently producing a segmented distribution of the barium in isolated dilated coils The opaque meal passes through the jejunum slowly and irregularly The filled areas show no evidence of peristalsis At times all of the barium that has left the stomach is collected in a localized segment while the remainder of the duodenum and jejunum are empty The invariable presence of these changes in active sprue strongly suggests that they contribute to the deficiency state by interference with absorption and thus tend to produce a vicious ascending spiral

SYMPTOMATOLOGY

Sprue is a disease that lasts for a number of years with alternate exacerbations and remissions hence the progress of the disease varies greatly in different individuals The disease begins insidiously with periods of diarrhea and more or less sore mouth When well established it manifests four important symptoms soreness of the mouth and tongue diarrhea with characteristic stools and gaseous distention of the abdomen progressive anemia and emaciation

Sensitiveness of the mouth is often one of the first symptoms of sprue and

it is almost always noted at some stage of the disease Acid or spiced foods cause discomfort Next the sides and tip of the tongue become red and superficial erosions develop along the borders of the tongue and buccal mucosa Later ulcers may form at the site of the rear molars (Crombie s ulcers) Still later the tongue becomes denuded of epithelium and is glazed and fissured and the mouth and throat are very sensitive The gums may also be tender This condition leads to an excessive secretion of the saliva which causes drooling to avoid swallowing These symptoms have led to the name psilosis for the disease Nutrition is much impaired because of the pain caused by eating and swallowing which cause a burning sensation beneath the sternum This restriction of food produces a real deficiency and consequently increases the symptoms in a truly vicious circle During remission these phenomena subside but it must be noted that some cases of sprue are wholly intestinal and never have these mouth and tongue lesions It must be remembered that for each classic case of the disease there may be ten atypical cases

The diarrhea of sprue is of two types acute and chronic and both are characteristic In the acute form the diarrhea is watery Some time after eating acid fruits or other food that disagrees with the patient the abdomen is distended the intestines gurgle and soon a large liquid stool and much gas are passed Three or four such stools may be passed during the day usually soon after meals although they may occur during the night The passage of these stools causes no pain but on the contrary a sense of relief it is obvious that the loss of this large amount of fluid results in a dehydration and in a diminution of weight Gradually the acute condition passes off and the chronic sprue stools commence These are no longer watery but are pasty and of enormous size They are always light colored sometimes almost white and are mixed with gas and leave a foul odor There may be only one such stool early in the morning but often there will be several during the day When examined microscopically they appear like normal stools except for the large amount of fat and particularly crystals of fatty acids Digestion has been normal but very little of this digested food can have been absorbed It has simply passed through the intestine decomposing and fermenting with the resulting massive foul pasty stool In all cases of sprue the absorption of fat is much reduced and causes steatorrhea With exacerbations of sore mouth the diarrhea increases and may return to the acute type

The anemia becomes a prominent symptom only after the diarrhea has lasted some time At first it is a simple anemia of the usual secondary type but as the disease progresses the anemia becomes macrocytic and profound not to be distinguished by blood studies from true pernicious anemia Red blood cell counts of from 1 500 000 to 1 000 000 are not uncommon at this time The first manifestation of these high degrees of anemia is increasing weakness and prostration with a total disinclination to go through the daily work followed later by a certain amount of breathlessness and other general symptoms of anemia Patients do not begin to complain of weakness until the erythrocytes have been diminished to about 2 000,000

Emaciation is a progressive manifestation of sprue and it is caused partly by voluntary restriction in diet but chiefly by lack of intestinal absorption of the food that the patient actually consumes It is in fact chronic starvation

Other characteristics of sprue cases are found on examination They usually have a basal metabolic rate of minus 10 to minus 20 and a low blood pressure The systolic pressure will often be as low as 100 to 95 It is quite possible that these changes are not the result of sprue but that sprue develops in the type of individual who as the result of hormonal inbalance has both low blood pressure and low metabolic rate I have suggested that these conditions may be caused by a hypo-active anterior pituitary

Cord changes have been found in a few cases by several observers but this finding is atypical and most investigators have never seen any symptoms of such degeneration the disease in this respect being quite different from pernicious anemia

DIAGNOSIS

Sprue is distinguished from pernicious anemia by the character of the diarrhea the emaciation low blood pressure and metabolic rate and by the presence of hydrochloric acid in the stomach It is true that in older individuals hydrochloric acid may be deficient or absent as in simple achlorhydric anemia But achlorhydria is no part of the picture of sprue and the presence of acid serves to distinguish that disease from pernicious anemia Also there is no jaundice in sprue while the lemon yellow color of pernicious anemia is fairly typical Sprue may be distinguished from pellagra by the fact that there are no cutaneous manifestations The distinction from early cases of pellagra without dermatitis may be difficult but the progress of the disease will leave no doubt

PROGNOSIS

In the old milk cure days prognosis was most guarded Early cases of sprue usually recovered after transfusion but the more advanced cases often died At the present time it may be said that if a patient is not actually moribund he can not only be saved but can look forward to recovering his usual degree of good health If sprue symptoms should return it is only necessary to resume liver therapy Many patients never suffer from sprue again after complete recovery but they should not return to the tropics It is well recognized that residence in the tropics results in a lowered basal metabolic rate and a lowered blood pressure It is possible that the consumption of an excess amount of food under these circumstances is part of the reason for the breakdown of intestinal absorption just as overburdening the pancreas may precipitate diabetes Whatever the explanation patients who have recovered from sprue should shun the tropics

TREATMENT

The modern treatment depends on the use of liver extract Some persons can take this by mouth but taken thus it is of little value in the more ad

vanced stages of sprue because it is not absorbed It is preferable in all cases to give the extract parenterally In order to correct the diarrhea much larger doses must be given than those used in pernicious anemia and it has been found that the relatively cruder extracts are more effective in sprue Intra muscular injections of 5 cc of crude liver extract every day or every other day is necessary during the first one or two weeks of therapy After the acute symptoms have subsided the dosage may be reduced to 5 cc twice weekly until the patient is well on the road to recovery If the patient is seriously ill or the blood count is markedly reduced a blood transfusion of 500 cc of whole blood may be given by either the direct or indirect method Whether or not it will be necessary to repeat the transfusion will depend on the response of the patient to the first transfusion and liver extract injection While the very highly refined extracts are effective in pernicious anemia they are relatively of no value in sprue Following the acute episode the dosage must be established for each patient and some advanced cases have required an injection of 1 cc daily or 3 cc to 5 cc. once or twice weekly over a period of several years before the extract could be safely discontinued The results of this treatment are miraculous The sore mouth disappears promptly and after a few days to several weeks the stools become formed possibly for the first time in years The diet during this treatment is high in protein low in fat and low in carbohydrate Meats generally are the first foods well absorbed next certain carbohydrate foods like potatoes and other starchy vegetables Vegetables and fruits must be tried in minute quantities and added to the diet when they are found harmless From this it will be seen that the return to a normal diet is a matter of experiment Breadstuffs and fats are probably the last articles to be tried Since such a diet is distinctly limited and quite deficient yeast and other vitamins particularly A and D must be administered daily Yeast particularly has proved valuable in the treatment of sprue because it supplies all portions of the B complex

Quite recently a body of evidence has accumulated indicating that the substance that relieves the sore mouth and checks the diarrhea is niacin and there are some claims that niacin cures sprue Since niacin has precisely this effect in pellagra it seems probable that it acts in the same way in sprue It cannot be said to cure sprue since in that disease there is undoubtedly a multiple deficiency But if the diarrhea can be checked the remainder of the deficiency may be made up in the diet if the other vitamins are added If niacin is in fact the vitamin that controls the diarrhea it becomes apparent why the cruder extracts of liver have proved most potent in treatment These crude extracts contain large quantities of niacin some analyses giving as high as 500 mg per cent and it was this fact that led to the use of nicotinic acid in pellagra In the more highly refined liver extracts the percentage of niacin is much reduced In the cases in which nicotinic acid has been used by mouth it has been found that about oo mg are required daily Obviously a much smaller dosage is effective when it is used parenterally as in liver extract The liver extract should in any case be tried first in all cases of macrocytic anemia The treatment with niacin is still in the experimental stage The treatment with liver extract is

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CHAPTER LIII

SCURVY

EDWARD B VEDDER

SCURVY IS CAUSED BY DEFICIENCY IN THE DIET OF VITAMIN C (ascorbic acid) which is widely distributed in fresh fruits vegetables and certain roots Scurvy is characterized clinically by anemia and great debility by a marked tendency to hemorrhages and by changes in the bones resulting in softening and fragility

HISTORICAL NOTE

What is generally regarded as the first good description of scurvy was written by the Sieur de Joinville of the Army of the Christian Crusaders in Egypt in about the year 1[illegible]60 There came upon us the sickness of the host which sickness was such that the flesh of our legs dried up and the skin of our legs became spotted black and earth color like an old boot and with us who had the sickness the flesh of our gums petrified nor could anyone escape from the sickness who had to die The sign of death was this that when there was bleeding from the nose then death was sure He also describes the marked debility and the tendency to faint on the slightest exertion

Scurvy was probably unknown among the sailors of ancient times because all their voyages were short With improvement in navigation and the discovery of the Indies scurvy appeared among the seamen and was particularly severe since there was no opportunity to obtain antiscorbutic food until they reached land Vasco da Gama who first found the passage to the East Indies around the Cape of Good Hope in 1497 lost 60 of his 100 men from scurvy Scurvy then continued for 400 years to be the most terrible disease of seamen

ETIOLOGY

The cause of scurvy is a deficiency in the diet of vitamin C (ascorbic acid) Pure vitamin C was first isolated in 1932 by Waugh and King In 1933 the structural formula was assigned by Hirst and his collaborators after which it was readily synthesized The synthetic product is in every way equivalent to the natural vitamin C Not only so it is much cheaper and is readily obtainable from commercial firms

accepted and we cannot afford to experiment with an extreme degree of anemia Indeed in very advanced cases the use of liver extract should be reenforced by blood transfusion

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Anasarca is almost as characteristic of human scurvy as the hemorrhages The enlarged heart and general anasarca in human scurvy as it appeared at sea was in my opinion due to deficiency of thiamin that is to wet beriberi complicating scurvy Nothing resembling these cardiac changes and anasarca are found in guinea pig scurvy

The liver is congested in all cases in which there has been cardiac failure The kidneys show the same picture of congestion mixed with hemorrhage and these hemorrhages are commonly seen in the adrenals Hemorrhage may al o occur from the bladder or urethra

Bones Fractures are common either ununited or healed with very large callus

Scurvy is a disease of the connective tissues Separation of the epiphyses is also common Subperiosteal hemorrhages are common in the femur and tibia Beading of the ribs is usual and separation of the cartilage at the costo chondral junction or from the sternum was described by Lind The teeth are subject to early softening Scurvy has also been produced in monkeys During experimental work conducted with monkeys I found that the large bones of the femur and tibia were soft and spongy so that they could be cut with a knife like a piece of soft wood The fatty marrow of the long bones is entirely re placed by red hematogenous marrow This corresponds with the blood picture of anemia with evidence of marrow response normablasts and macroblasts in considerable numbers

SYMPTOMATOLOGY

Depletion Period As usually observed in man the depletion period is from four to seven months

Observations were made by Crandon Lund and Dill 1940 in which one of these observers spent six months on a diet deficient in ascorbic acid The plasma level of ascorbic acid fell rapidly and was zero after forty days Yet it was thirteen weeks more before hyperkeratotic papules the first clinical evidence of scurvy appeared and still another month was required before perifollicular hemorrhages occurred that is five months and eleven days after the commence ment of the diet In earlier days scurvy would hardly have been diagnosed so soon

Mode of Onset Before the onset of definite clinical symptoms of scurvy there is a period of debility weakened resistance to disease and imperfect healing of wounds This condition has been called latent or subclinical scurvy Detection of these cases has been attempted by such methods as the capillary resistance test This test is positive in scurvy but may also be positive in other diseases The titration of the amount of ascorbic acid in the blood plasma and the amount excreted in the urine following the administration of a given amount of ascorbic acid are other methods that have been used The normal amount of ascorbic acid in the blood ranges from 0 7 to 1 4 mg per 100 cc. The ascorbic acid saturation test is a more accurate estimate of the vitamin C in the tissues

PATHOLOGY

Good descriptions of gross pathology were given by the older writers particularly Lind In later years such studies have been made by Aschoff and Koch Wolbach and Howe have contributed the best pathologic study of scurvy in guinea pigs

The basic lesion in scurvy is the degeneration or failure of production of the intracellular cement substance or collagen of the connective tissues and the pathology and symptomatology of pure scurvy are due to this lesion in the connective tissues It results in the softening of the bones and teeth and the loss of the cement substances between the endothelial cells of the capillaries results in hemorrhages that are characteristic of scurvy But it is doubtful whether pure scurvy has ever existed except in the experimental guinea pi The diets used by sailors i e salt meat and sea biscuit must have been deficient not only in vitamin C but in vitamin A thiamin and possibly in other vitamins Infantile scurvy has often been confused with rickets

Rigor mortis is slight and decomposition occurs readily The skin is pale and is dotted with hemorrhages which vary in size from pin point petechiae to large ecchymoses They occur most often in the lower extremities although they may be on any part of the body Trauma to which the legs are most subject is important in their production In infants the inner aspect of the thighs is a common location owing to the rubbing of the diaper The hemorrhagic spots are of all colors red for the recent changing to blue and green for the older lesions

Subperiosteal hemorrhage is characteristic particularly in children and abdominal hemorrhages may simulate appendicitis or a new growth Hemorrhages seldom occur in the lungs or the central nervous system The lungs are often congested but are otherwise normal

Alimentary Tract The gums are greatly swollen ulcerated and necrotic the teeth are loose and may fall out Profuse hemorrhage may occur from any part of the alimentary tract

Stomach Congestion of the mucous membrane with small superficial erosions is present

Duodenum Congested and small duodenal ulcers are frequent and are a source of intestinal hemorrhage This picture is continued throughout the small intestine Bleeding from any of the mucous membranes is common in fatal scurvy Many have died after profuse hemorrhages from the nose or rectum Some of this coagulated blood is found post mortem in the gastro intestinal tract

Heart Many scurvy patients die suddenly after a slight exertion and in these cases of heart failure the heart is enlarged There is hypertrophy of the right and the left ventricles and the right ventricle and auricle are dilated This observation was not only common in adults but the same changes have been described in 21 of 31 necropsies in infants

Hemorrhages Scorbutic patients are subject particularly in the late stages of the disease to profuse external hemorrhages from various parts of the body such as the nose the gums the intestines and the genito urinary tract and also from the ulcers Hemoptysis hematuria and hematemesis occur more rarely Bleeding from the bowels is relatively common and is often seen in scorbutic guinea pigs

Effusions of bloody fluid into the pericardium or pleural cavities are not uncommon Such accidents are followed by pain dyspnea great weakness and the usual physical signs of fluid in these cavities Ascites also occurs In many cases the legs become edematous at first swelling only in the evening but later the edema is constant and pits on pressure These effusions and anasarca are believed to be a manifestation of wet beriberi complicating scurvy

Bones Hemorrhages occur under the periosteum especially in the leg bones in children The shaft of the bones becomes spongy and fragile The bones most frequently and most severely affected are the tibia and femur particularly near the knee and ankle joints the ribs and the lower jaw This bone degeneration causes continual racking pain and disability Muscle pains separation of epiphyseal junctions and ulcers combine to make scurvy more painful than almost any other disease Although patients have a clear mind until the end they usually suffer from great mental depression melancholy and despondency

Death may be due to a sudden cardiac failure after any unusual exertion Death may also be due to a sudden fatal hemorrhage to a sudden pericardial or pleural effusion to pulmonary edema or to intercurrent infections Such infections are by no means rare and as a result more than one investigator has believed that a considerable part of the scorbutic picture is caused by infection We now believe that these are only terminal incidents to which scorbutic patients are more than usually subject because of lack of resistance the large amount of stagnating blood and the anemia The amount of complement in the serum is reduced in scorbutic guinea pigs

DIAGNOSTIC METHODS

Blood Anemia is always present and may be severe The blood picture is that of secondary anemia In early cases the erythrocytes fall to from 4 000 000 to 3 000 000 with the hemoglobin relatively lower Later especially if hemorrhages are severe the red cells sink very low In one case 557 000 was recorded and in another 370 000 Nucleated cells are often present in considerable numbers Normoblasts are chiefly found but microblasts and megloblasts also occur In this condition the blood smear resembles pernicious anemia but the color index is low and the blood condition is not a true macrocytic anemia Moreover the leukocyte count is frequently though not invariably increased and counts from 20 000 to 50 000 have been recorded The granulocytes are relatively decreased and there is a considerable increase in large lymphocytes and monocytes

The coagulation time is shorter than normal seldom longer than one minute and when the clot forms it is firm and dense The bleeding is due to the injury to the capillaries This has led to the use of the capillary resistance test

The earliest clinical symptoms of scurvy are loss of weight with languor dizziness and fatigue on the slightest exertion The complexion is pallid or yellowish Soon in addition to the fatigue there are breathlessness and dull aching pains in the legs and feet Because this pain is referred to the long bones and larger joints it may lead to the diagnosis of rheumatism A common complaint is stiffness of the knees with feebleness of the leg muscles Diarrhea may occur at this early stage and diarrhea or dysentery is common when scurvy is fully developed

Gums The changes in the gums are one of the most constant early and characteristic features of the disease At first there are fungous elevations between the teeth that have been called scurvy buds These extend until the gums are generally swollen red and spongy and bleed upon the slightest provocation This swelling is at least in part due to hemorrhage into the gums It begins first and is most intense in the lower jaw usually beginning around the molar teeth and progressing forward The swelling continues until the gums around the molars rise to the level of the teeth after which the swollen and spongy tissue ulcerates and breaks down often sloughing away until the necks of the teeth are left bare The teeth become loose and often fall out partly because of loss of gum tissue and partly because of softening of the bony structure of the alveolus Mastication becomes impossible and the diet must be restricted to soft foods and liquids a requirement that was exceedingly difficult at sea The breath is exceedingly foul and offensive

Hemorrhagic Diathesis Soon after the earliest symptoms appear the tendency to interstitial hemorrhage becomes marked and the symptomatology of the disease depends chiefly on the number location and amount of these hemorrhages The more usual locations are the skin and the muscles

Skin The characteristic hemorrhages appear first as petechial spots often about the hair follicles Later these spots become larger from the bigness of a lentil to that of a handbreadth and bigger They become purplish and later greenish blue to yellow as they become absorbed These spots are not painful or tender to pressure but later in the course of the disease there is a tendency of these hemorrhagic areas to ulcerate after the slightest scratch or injury The edges of such an ulcer are swollen and livid and the bottom is covered with exuberant granulations It is particularly important not to mistake these ulcers for syphilitic ulcers

Muscles Diffuse interstitial hemorrhage into the muscles is exceedingly common particularly into the muscles of the leg and thigh and around the knee joint The stiffness and weakness of the knees early in the disease are probably caused by the effusion of blood into this region As the blood coagulates it causes swelling of the legs and the knees become fixed in a flexed posture Finally there may be a brawny hemorrhagic infiltration of both muscles and subcutaneous tissue that causes absolute fixation of the knee If dietary relief is not obtained concomitant bony changes take place with the result that the joint becomes ankylosed These muscular hemorrhages cause violent racking pains and tenderness on pressure and walking becomes impossible

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Death may be due to a sudden cardiac failure after any unusual exertion Death may also be due to a sudden fatal hemorrhage to a sudden pericardial or pleural effusion to pulmonary edema or to intercurrent infections Such infections are by no means rare and as a result more than one investigator has believed that a considerable part of the scorbutic picture is caused by infection We now believe that these are only terminal incidents to which scorbutic patients are more than usually subject because of lack of resistance the large amount of stagnating blood and the anemia The amount of complement in the serum is reduced in scorbutic guinea pigs

DIAGNOSTIC METHODS

Blood Anemia is always present and may be severe The blood picture is that of secondary anemia In early cases the erythrocytes fall to from 4 000 000 to 3 000 000 with the hemoglobin relatively lower Later especially if hemorrhages are severe the red cells sink very low In one case 557 000 was recorded and in another 370 000 Nucleated cells are often present in considerable numbers Normoblasts are chiefly found but microblasts and megloblasts also occur In this condition the blood smear resembles pernicious anemia but the color index is low and the blood condition is not a true macrocytic anemia Moreover the leukocyte count is frequently though not invariably increased and counts from 20 000 to 50 000 have been recorded The granulocytes are relatively decreased and there is a considerable increase in large lymphocytes and monocytes

The coagulation time is shorter than normal seldom longer than one minute and when the clot forms it is firm and dense The bleeding is due to the injury to the capillaries This has led to the use of the capillary resistance test

Capillary Resistance Test This test was originated by Wright and Lilienfeld in 1936 It is carried out by placing the arm band of a blood pressure instrument about the arm and inflating it until the pressure reaches midway between systolic and diastolic pressures It is maintained at this level for fifteen minutes and then released Count the number of petechiae on the forearm visible to the naked eye in a circle about 1.5 cm in diameter placed 4 cm below the bend of the elbow Up to fifteen petechiae are considered within normal range

Vitamin C saturation has been studied by Wright and MacLenathen (1938) and found to be a better measure of ascorbic acid deficiency than either the capillary resistance test or ascorbic acid blood plasma level In this test the patient is studied in the fasting condition One thousand milligrams of ascorbic acid are given by intravenous injection and urine specimens are examined one and one half hours three hours and five hours after the injection An excretion of more than 450 to 500 mg of ascorbic acid in five hours is considered as within normal range thus indicating that the tissues have sufficient ascorbic acid content and the excess is excreted While most common in individuals suffering from active or latent scurvy this test is by no means pathognomonic and cannot be used without other checks as evidence of deficiency in vitamin C intake

COMPLICATIONS

Pneumonia is a frequent complication that terminates the illness Other infectious diseases such as dysentery typhoid typhus and malaria were by no means uncommon among sailors Because of their debilitated condition persons suffering from scurvy are rendered peculiarly susceptible to infections

DIAGNOSIS

The early changes in the gums have been mistaken for pyorrhea although the scurvy buds are completely different from the changes produced by pyorrhea The stiffness and pains in the limbs and joints have been mistaken for rheumatism or some form of arthritis The subcutaneous hemorrhages can be mistaken for one of the various forms of purpura No dietary deficiency is responsible for purpura there is no diminution of platelets in scurvy and neither the coagulation time or the bleeding time is increased in scurvy A therapeutic test will settle the question for if the disease is scurvy the symptoms will disappear promptly after the administration of either orange juice or 50 mg of synthetic ascorbic acid for several days

PROGNOSIS

The prognosis as to life is exceedingly bad unless the patient s diet is changed With the proper treatment practically all patients recover promptly

But there are great individual differences in susceptibility All men do not develop scurvy at the same time although living on the same diet and some will die before others become seriously ill This is probably because some are able to hold ascorbic acid in the tissues better than others

TREATMENT

In the treatment of active scurvy the patient should be kept in bed to avoid the danger of sudden death caused by exertion He should be given a diet of milk with five or more 6 ounce tumblers of fresh orange juice daily This will afford approximately 500 mg of ascorbic acid daily As soon as the gums and teeth have returned to normal meat potatoes and fresh vegetables are added to his diet The results are miraculous for in a few days all clinical signs of scurvy disappear Ascorbic acid 100 mg three times daily in tablet form is indicated it also may have to be given by intravenous injection But it must not be supposed that the patient returns to normal so rapidly Time must be allowed for the complete repair of bone and connective tissues

At present the course of treatment may be studied by the excretion of ascorbic acid in the urine This will not occur to any considerable extent until the tissues have become saturated with ascorbic acid Blood counts and the capillary resistance test may also be used as tests of recovery When these are normal and when a daily intake of 50 mg of ascorbic acid is assured for the future the cure will continue automatically Attention must also be paid to correcting the deficiency of other vitamins particularly thiamin the B complex and vitamin A This may be accomplished after the first few days by prescribing a diet adequate in these essentials

PROPHYLAXIS

Prophylaxis is reduced to the simple expedient of obtaining approximately 50 mg of ascorbic acid daily from the foods consumed This amount will be supplied in 100 gm of fresh citrus fruits (oranges lemons grapefruit) Limes are distinctly inferior as an antiscorbutic and bottled lime juice is practically worthless The following figures obtained by titration with dichloro benzenol indophenol per each 100 gm of food may be quoted Tomato juice 0 040 cabbage 0 050–0 100 turnip greens 0 030 spinach 0 030–0 100 green peas 0 020 potato 0 020 green beans 0 01 Brussels sprouts 0 070 cauliflower 0 050 lettuce 0 05 (higher in green leaves) apples 0 002 pineapple juice 0 040 rhubarb 0 030 parsnips 0 030 turnips 0 030 milk 0 002

Although the content of ascorbic acid is in nearly all cases considerably reduced in cooking either by bleaching or oxidation it is obvious that anyone who eats a mixed diet with a reasonable allowance of fresh fruits and vegetables is receiving an adequate dose of ascorbic acid While the amount of ascorbic acid must be relatively small in potatoes as they are ordinarily cooked yet it is of importance because of the considerable quantities of potatoes consumed The same may be said of milk which is a poor source of ascorbic acid for at best it has not more than 25 mg per liter Human milk contains from 4 to 7 mg per cent or two to three times as much as fresh cow s milk Thus it is easy to understand why infantile scurvy is uncommon in infants receiving their mother s milk and why it has continued to occur frequently on a diet of modified cow s milk Such infants must be given an ounce of orange juice daily

It has been known ever since the original experimental work of Holst and Froelich that some canned foods such as cabbage and tomatoes retain a considerable part of their ascorbic acid Heat without oxidation does not destroy this vitamin and as foods are now sealed in cans before processing canned foods retain a considerable proportion of their original ascorbic acid. Hess used canned tomato juice successfully in the treatment of infantile scurvy and this is therefore suitable for the use of those who are too poor to buy fresh orange juice But dried fruits and vegetables are completely deprived of ascorbic acid by the slow oxidation involved in the drying process and should never be used as antiscorbutics

Fresh meat is also relatively poor in ascorbic acid though when not over cooked and eaten in large amounts meat too will prevent scurvy Liver and kidney are very rich in ascorbic acid Liver contains at least as much vitamin C as fresh cabbage and frying does not destroy it

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SECTION EIGHT

DISEASES CAUSED BY YEASTS AND FUNGI

CHAPTER LIV

INTRODUCTION

MORRIS MOORE

MYCOLOGY IS THE STUDY OF A COMPLEX LARGE HETEROgeneous group of organisms termed fungi These are non chlorophyll bearing plants characterized by certain fundamental morphologic properties Fungi differ from other plants in that they are not differentiated into roots stems or leaves but grow as an irregular mass of vegetation known as a *thallus* Consequently they are considered to be members of the phylum *Thallophyta*

Fungi develop characteristic structures which distinguish them and relegate them to groups or subdivisions As distinguished on the one hand from Schizomycetes or bacteria in the general sense and on the other hand from Myxomycetes or slime molds pathogenic fungi may be divided into filamentous and yeastlike organisms The filamentous group shows chains or septate filaments comprised of spherical cylindrical club shaped or rectangular cells surrounded by cell walls These filaments are termed *hyphae* They are vegetative structures which when seen collectively or as a mass are known as *mycelium* Hyphae start as protuberances of the filament a process of sprouting These extensions increase in size and are separated from the parent hypha by a septum or cross wall Daughter cells or sprout cells arise in similar fashion but these increase in size round up are cut off by a septum and are termed *blastospores* This type of vegetative growth is common among yeasts or yeast like organisms In a medium unfavorable to the propagation of the fungi a thick wall is formed around the contracted protoplasm of the cell to form resting cells or *chlamydospores* When conditions for growth are again favorable the *chlamydospores* germinate to form normal vegetative mycelium

Yeasts or yeastlike organisms show a vegetative thallus which may consist only of blastospores or budding cells or they may be made up of hyphae blastospores and various specialized organs many of which are termed *spores* These are cells or groups of cells which are thin walled structures round or elongate and capable of germinating to give rise to new growths Spores are either sexual resulting from the fusion of two cells or they may be asexual

The classification of fungi is based on the presence or absence of the perfect stage the process of fertilization and the reproductive structures Where the

fertilization process is unknown or partially known the fungi are termed imperfect and are placed in a separate group

CLASSIFICATION OF FUNGI

Thallophyta

I *Algae* Chlorophyll bearing structures which are able to derive nutriment from carbon dioxide in the air or as a result of the action of sunlight

II *Fungi* Do not bear chlorophyll consequently must obtain food from plant and animal matter

A SCHIZOMYCETES Bacteria in the general sense

B MYXOMYCETES Slime molds resembling protozoa and made up of a vegetative body with a naked multinucleate plasmodium

C EUMYCETES *or true fungi*

1 *Phycomycetes* United protoplasts (elementary cells) form a single large cell (zygote) which produces *zygospores* Hyphae non septate in vegetative stage

2 *Ascomycetes* Reproduction by a common method of spore formation *endospores* within a sac termed the *ascus* Spores called *ascospores* Hyphae septate in vegetative stage

3 *Basidiomycetes* Spores borne on a specialized organ termed the *basidium* which forms *basidiospores* Hyphae septate

4 *Fungi Imperfecti or Hyphomycetes* Life cycle unknown and sexuality lost Free spore formation Hyphae septate

The following additional structures characterize the true fungi *arthrospores* cells or thallospores which separate from the parent hypha and are capable of developing into new hyphae *sporophore* a specialized structure that bears spores *conidia* asexual cells oval spherical or pear shaped which arise laterally or terminally on a hypha by budding and are cut off by a septum *sporangium* an endospore bearing cell borne on a *sporophore* *sporangiophore* a sporangium bearing sporophore *sporangiospore* non motile spores enclosed in a sporangium *conidiophore* a sporophore with the spores abjointed exogenously at the tip *sterigma* a specialized hyphal structure to which a spore is attached *spiral* a coil like or corkscrew formation of a hyphal appendage or tendril without reproductive powers *racquet mycelium* an enlarged section of a hypha (racquet shaped) attached to the narrow portion of the adjoining hyphal cell and separated by a septum *fuseaux* elongated fusiform or blunt end multiseptate cells forming chambers which are capable of reproduction *nodular organs* knotted or entwined hyphal strands which may form around the parent hypha or as isolated enlargements (suggestive of sclerotia) *sclerotia* small hard compact masses made up of hyphae and cells developed under unfavorable conditions for growth *pectinate bodies* hyphal branches with unilateral abortive projections simulating irregular teeth of a comb

Although a botanical classification based on the characters of the fungi (cultural biologic and microscopic) is the truly scientific logical method for differentiating these organisms a practical medical classification for clinical

purposes has been added in the past This system based on invasiveness and anatomic distribution has the following divisions

(1) Superficial mycoses affecting only the stratum corneum of the skin and the hair never becoming invasive or systemic

(2) Dermatomycoses involving and invading the superficial and deep layers of the skin and also the hair and the nails No evidence of systemic involvement

(3) Mycoses usually primarily involving the skin or mucous membranes or both systemic invasion being either primary or secondary

(4) Systemic infections chiefly primary with occasional or rare secondary cutaneous involvement

LABORATORY PROCEDURES

The investigation for the presence of pathogenic fungi and then their cultivation on artificial media to determine genus and species are important adjuncts to the subsequent prophylactic measures in mycotic infections

The usual method used for the examination of skin scrapings hair pus or sputum is to mount the suspected material in 10 to 30 per cent hydroxide solution either sodium or potassium on a clean glass slide heat gently press a coverslip over the mixture and examine at once A weak solution takes longer to clear the material than a stronger solution The fungous elements appear clear In examining material by this method care should be taken not to confuse the artefacts such as crystals mosaic fungus and distorted fat globules with the fungus spores and hyphae

If the material is not too thick the following method presents a clear picture and is less confusing Stir the suspected material into a drop of 1 per cent aqueous methylene blue placed on a clean glass slide heat gently until the mixture steams place a clean coverslip over the preparation and press down gently to flatten out the material and express the excess solution blot excess solution then add a drop of glycerin along one edge of the coverslip and heat gently The glycerin will clear the tissue and push out the excess methylene blue which is taken up by filter paper The fungi stain blue by this method

The cultivation of suspected material is also important For this procedure we are indebted to Sabouraud who contributed greatly to the cultivation of pathogenic fungi It is almost impossible to duplicate the original formulas for media used by Sabouraud since most of the ingredients cannot now be obtained Accordingly the following media are advocated since they yield uniformity in cultural features and employ standard products

Sabouraud s Agar

Bacto-dextrose or maltose	40 gm.
Bacto-peptone	10 gm
Bacto-agar	15 gm
Distilled water	1 000 cc

Dissolve ingredients tube sterilize at 15 pounds pressure for twenty minutes then slant The resulting medium has a pH of approximately 5 6 Either maltose or glucose may be used Maltose medium is slightly better for isolation purposes but the glucose agar shows more pronounced gross characteristics of the fungi (color convolution ridges etc)

Conservation Agar

This medium is made up in the same way except that the sugar is omitted It is a useful medium for stock cultures since colonies do not tend to become pleomorphic on it

Corn Meal Agar

Yellow corn meal	40 gm
Agar	15 gm
Distilled water	1 000 cc

Add the corn meal to 500 cc water and heat for one hour at 65 C Filter through paper Dissolve the agar in the remaining 500 cc then mix with the corn meal extract Tube and autoclave for twenty minutes at 15 pounds pressure then slant tubes

This medium is very useful for differentiating filamentous forms from non filamentous yeasts and for the elaboration of the various morphologic structures of the dermatophytes

Wort Agar

This medium may be obtained already prepared as a product of the Digestive Ferments Co The formula is as follows

Maltose Tech Difco	12 75 gm
Malt extract Difco	0 15 gm
Dextrose Difco	2 75 gm
Glycerol	2 35 gm
Dipotassium phosphate	1 00 gm
Ammonium chloride	1 00 gm
Bacto peptone	0 78 gm
Bacto agar	15 00 gm

Suspend 50 gm of this preparation in 1 000 cc cold distilled water Boil for a few minutes to dissolve the medium completely Tube and sterilize for fifteen minutes at 15 pounds pressure then slant The medium has a pH of approximately 4 8

This medium is especially adapted for the isolation and differentiation of yeasts and yeastlike organisms since it tends to inhibit the growth of bacterial contaminants

There are a number of methods for the further study of fungi for which the reader is referred to Dodge s textbook on *Medical Mycology*

The references for this and subsequent chapters in this Section are included in the *Bibliography* on pages 739 to 746

CHAPTER LV

SUPERFICIAL MYCOSES

MORRIS MOORE

PITYRIASIS (TINEA) VERSICOLOR

PITYRIASIS (TINEA) VERSICOLOR (CHROMOPHYTOSIS DERmatophytosis furfuracea *Kleienflechte* pseudo liver spots) is a chronic stubborn recurrent infection of the superficial layer of the epidermis (stratum corneum) caused by *Malassezia furfur* The disease manifests itself as a follicular or macular eruption on the body arms and thighs and occasionally on the scalp of fawn to chamois colored branny or furfuraceous lesions

ETIOLOGY

Malassezia furfur (Robin) Baillon 1889 when seen in the stratum corneum of young lesions consists of a fine branching mycelium 1 5 to 2 microns in diameter As the lesions become older the hyphae develop cross walls to form short hyphal cells 1 5 to 4 microns in diameter and 10 to 16 microns in long axis These cells in turn become spherical free arthrosporous cells 3 to 8 microns in diameter and are observed associated with the filaments in old lesions

On artificial media although not easily grown the fungus develops first as spherical budding cells which germinate to form fusiform cells These then produce cross walls become elongated and branch The cultures on media develop as flat and dull or moist mucoid and shiny verrucous cerebriform to rugose vermiculate and somewhat velvety colonies with the color varying from whitish gray and fawn to creamy buff and light cinnamon in young colonies to ochraceous buff and dark cinnamon in older cultures As the growth becomes much older the organism loses its pigment Microscopically the fungus in subculture shows a characteristic development from the spherical cells to fusiform segmented cells then to hyphae The filaments become beaded to form oidioid structures which are walled off and arthrosporous and then spherical ellipsoid or ovoid and thick walled the latter are the blastospores seen in scrapings from an infection

EPIDEMIOLOGY AND GEOGRAPHICAL DISTRIBUTION

The disease is not known to occur in epidemic form although several cases have been known to occur in families following the primary infection of one



Fig 69 A Pityriasis (tinea) versicolor of the follicular type B Section of lesion of pityriasis (tinea) versicolor Note filaments and blastospores in stratum corneum Similar forms appear in scrapings examined under the microscope

of the members Pityriasis versicolor is widespread throughout the world It is rare in children and old people but is prevalent in young and middle aged individuals particularly those who perspire profusely and neglect their general cleanliness

PATHOLOGY

There may be inflammation of the lesions when they occur on a delicate skin or on a seborrheic base The patches become pink in color somewhat raised and pruritic resembling pityriasis rosea (Fig 69) With the fungus never found below the horny layer of the skin the histopathologic picture is usually confined to that of mild inflammation or edema and slight thickening of the rete malpighii

SYMPTOMATOLOGY

There are no subjective symptoms Occasionally there may be slight itching which becomes marked in hot weather The lesions appear first as small

irregular or spherical fawn or chamois colored spots which develop into irregular maculae spreading or increasing peripherally They may begin in the hair follicles growing up and around the hairs to produce the follicular type of the condition The more usual form the macular type is formed by the coalescing of small spots to develop large irregular plaques with at times well defined borders which may be somewhat raised in old lesions A fine branny scaliness or furfuraceous condition of the patches changes in the older lesion from a fawn or light brown color to a dirty grayish white The color of the infected area varies at times on different individuals being darker on some (*tinea nigra*) and lighter on others (*tinea alba*) This may be due to the age and number of spores present to the type of secretion or to the amount of glucose excreted This is particularly evident in warmer climates

The lesions are chiefly seen on the trunk involving the chest back neck and arms rarely on the lower extremities chin or face It is more marked over the sternum less marked on the sides It may be seen in the axillae spreading to the elbows and in the genitocrural region spreading to the knees

The disease is recurrent in spite of treatment seeming to disappear in the winter but reappearing in the spring

DIAGNOSIS

The disease is usually diagnostic in itself because of the color and character of the lesion the chronicity of the disease and the usual lack of subjective symptoms Diagnosis is easily confirmed by finding the characteristic groups of spores and short filaments in from 20 to 30 per cent potassium hydroxide mounts The finding of the typical organisms clearly differentiates this disease from such lesions as vitiligo leukoderma and melanoderma seborrheic dermatitis macular syphilis and pinta with which it may be confused The clinical entity of *pseudoachromia parasitica* is a form of tinea versicolor in which islands of unaffected skin are tanned by action of the sunlight while the skin underlying the area of infection remains white The masses of fungus spores and filaments do not allow the ultraviolet rays to affect the underlying skin When the affected area loses the furfuraceous condition the skin appears as islands of leukoderma

PROGNOSIS AND TREATMENT

If left untreated the disease will continue as large plaques Frequent scrubbing with soap and water may be helpful The daily sponging of a *saturated aqueous solution of sodium hyposulfite* preceded by a hot bath is usually effective but must be continued until complete eradication of the fungus takes place *Stubborn cases can be treated by allowing the hyposulfite to dry on the* skin and then applying • per cent hydrochloric acid This should be allowed to dry for about an hour then the body should be given a thorough bath This treatment should be applied daily for from one to two weeks then the simple saturated solution of sodium hyposulfite Treatment must be continued for at least three months after the lesions have apparently disappeared

EPIDEMIOLOGY AND GEOGRAPHICAL DISTRIBUTION

The disease is not known to occur in epidemic form although several cases have been known to occur in families following the primary infection of one



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SYMPTOMATOLOGY

There are no subjective symptoms Occasionally there may be slight itching which becomes marked in hot weather The lesions appear first as small

of the lesion pigmentation of the skin and as in pityriasis versicolor to the type of excretion on the skin of the patient As the patches enlarge they become greasy to the feel with a furfuraceous scaliness noticed particularly at the slightly raised somewhat reddened periphery



Fig 70 Erythrasma in the axilla

The eruption is found chiefly in the genitocrural region and in the axillae (Fig 70) but may be seen in the submammary folds in stout individuals or rarely in the flexures of the large joints locations where there is a great amount of perspiration and friction As a result of the constant pressure from opposing parts there may be some itching with a subsequent secondary inflammation due to scratching

DIAGNOSIS

The objective characteristics of erythrasma serve usually to distinguish it from other dermatoses The color and distribution of the lesions and usual ab-

ERYTHRASMA

Erythrasma is a sharply marginated and demarcated fawn to chamois colored at times furfuraceous lesion occurring in the axillae groin intergluteal cleft and other intertriginous areas and is caused by *Actinomyces minutissimus* (Burchardt) Brumpt 1927

ETIOLOGY

A minutissimus when seen in scrapings stained with methylene blue from a lesion or in biopsy specimens with the organism located in the stratum corneum consists of straight or curved rodlike bacilli the bacillary form of *Actinomyces* These rods may also be seen as beaded forms which disintegrate to form groups or chains of coccoid bodies or spores In young lesions the fungus is seen as a septate rarely branching mycelium of fine filaments approximately 0 6 to 1 3 microns in diameter which are easily dissociated into bacilliform arthrospores approximately 5 to 15 microns in length

The organism has rarely been cultured Michele reported cultures which gave a brownish color on gelatin and a wine red pigment on potato medium Ducrey and Beale obtained white cultures on gelatin and a reddish brown growth on potato These authors state that they have obtained lesions of erythrasma by artificial inoculation of human skin

EPIDEMIOLOGY AND GEOGRAPHICAL DISTRIBUTION

Erythrasma like pityriasis versicolor is not highly infectious and is not known to occur in epidemic form Not much is known about the method by which the disease is spread or about the predisposing factors involved Like pityriasis versicolor lack of personal cleanliness seems to aid the fungus in gaining a foothold on the human skin The disease seems to be world wide in its distribution It is more common in Europe and in tropical countries than in the United States where it is seen only sporadically Erythrasma occurs usually in adult males rarely in females and almost never in children

PATHOLOGY

Since the fungus is found only in the horny layer it produces little damage to the underlying tissue per se However as a result of scratching perspiration and friction caused by opposing parts there is usually inflammation which affects the epidermis and the cutis

SYMPTOMATOLOGY

Erythrasma starts usually as a macular eruption of small punctiform to large irregular or circular lesions which are non inflammatory in character producing no subjective symptomatology As the lesions mature they become sharply marginated brownish reddish yellow somewhat orange reddish brown or fawn colored plaques slightly raised above the surface of the skin resembling somewhat pityriasis (tinea) versicolor The color varies according to the age

The two principal species *P hortai* and *T giganteum* may be described as follows *P hortai* nodules in 20 to 30 per cent potassium hydroxide when compressed between a slide and coverslip manifests itself as a mass of rectangu



FIG 71 Piedra of Brazilian type

lar linear cells up to approximately 7 micron in diameter and 10 to 12 microns in the long axis Within the mass of cells are seen spherical to ovoid asci up to 30 microns in diameter with eight elongate ascospores measuring approximately 30 to 15 by 6 to 8 microns with long filiform appendages approximately 15 to o microns in length The whole mass although simulating macroscopically a sclerotium is actually analogous to a perithecial structure

In culture (Sabouraud's agar) the growth is seen as small dark brown colonies with a velvety appearance and a lighter margin which is adherent to the substratum The growth becomes rugose After ten weeks the colony becomes black

T giganteum on the other hand when examined as a crushed granule shows a number of spherical thick walled cells approximately 10 to 1° microns in

scence of subjective symptoms differentiate this disease from pityriasis versicolor From tinea cruris erythrasma is differentiated by the presence of marked inflammation and satellite lesions in the former Erythrasma is usually chronic without increase in symptomatology whereas tinea of the groin axillae or other intertriginous areas caused by dermatophytes or yeastlike organisms spread or show vesicles and other changes To definitely establish a diagnosis of erythrasma however the organism should be demonstrated This is usually difficult and requires staining with methylene blue and searching for the fungus with the oil immersion objective

PROGNOSIS AND TREATMENT

Erythrasma is a chronic and resistant disease and unless all affected areas are treated intensively is prone to relapse and recur The hair in the affected location should be shaved and antiparasitic treatment instituted The medication of choice is an aqueous saturated solution of sodium hyposulfite applied daily to the lesion As a prophylactic measure thorough daily washing with soap and water is advised with the subsequent application of the sodium hyposulfite solution for several months after the symptoms have disappeared In stubborn cases the following ointment is very valuable

℞	Salicylic acid	3 per cent
	Pyrogallic acid	4 per cent
	Ichthyol	2 per cent
	In white vaseline	
Sig	Rub into patches morning and night	

Watch for dermatitis—inflammation and burning Should that occur use amyli compound with 1 per cent phenol until irritation subsides then reapply pyrogallic ointment

PIEDRA

Piedra (Fig 71) is a nodular growth on the hair of the scalp beard or axilla with the production of cream colored soft and mucoid or hard and brittle nodules (Colombian piedra) and caused by members of the genus *Trichosporum* (*T giganteum*) or hard black and brittle nodules (Brazilian piedra) caused by *Piedraia* (*P hortai*)

Trichosporosis trichosporosis tropica trichosporosis indica trichosporosis nodosa piedra nostras tinea nodosa *Trichomycose nodulaire* (French) are the same or closely related diseases

ETIOLOGY

A number of species of fungi have been described as producing the nodules on hair These include *Trichosporum beigelii* (Rabenhorst) Vuillemin 1902 *T ovale* Paoli 1913 *T ovoides* Behrend 1890 *T glycophile* Dubois 1910 *Piedraia hortai* (Brumpt) Fonseca and Area Leao 19 8 *P sarmentoi* Perreira 1930 *P surinamensis* Dodge 1935 *P colombiana* Dodge 1935 *P venezuelensis* Brumpt and Langeron 1934

piedra affecting hairs of scalp axilla and beard produced by species of *Piedraia* (*P hortai*) Dubois in 1910 described *Trichosporum glycophile* which produced nodules in the pubic hair of a diabetic

PROGNOSIS AND TREATMENT

The disease is usually of long duration showing no tendency to disappear spontaneously A useful method of treatment is to sponge the hair with benzene to remove as many particles as possible wash it thoroughly with soap and water and then apply bichloride of mercury (1 1000) daily for several weeks The danger of a bichloride dermatitis should be considered If it occurs a soothing ointment should be used If the disease persists after this treatment, it is best to shave off the hair and then treat the scalp with a mild antiseptic

TRICHOMYCOSIS AXILLARIS FLAVA RUBRA ET NIGRA

Trichomycosis axillaris [lepothrix (Wilson) chromotrichomycosis Castellani s disease trichomycosis palmellina (Pick) trichomycosis nodosa (Patterson) trichomycosis chromatica trichomycosis vulgaris nodositas pilorum microphytica and trichonocardiasis axillaris] is a nodular growth on the hair of the axillae and at times on the hair of the groin It is caused by *Actinomyces tenuis* either alone or in symbiosis with pigment producing cocci

ETIOLOGY

Although all of the earlier workers agreed that some parasite was responsible no particular organism was agreed upon Patterson believed the agent to be a small bacillus Eisner and Sonnenberg a gram positive diplococcus Schobl a gram positive bacillus of the Corynebacterium type Waldeyer and also Ducrey a fungus Castellani established the agent as a fungus *Actinomyces tenuis* (Castellani) Dodge (*Nocardia Discomyces Streptothrix Cohnistreptothrix*) which he first called *Nocardia* then *Cohnistreptothrix* but this was changed by Dodge to *Actinomyces tenuis* This organism is found in the flava variety but in the rubra variety the fungus is associated with a red pigment producing coccus *Micrococcus* (*Rhodococcus*) *castellanii* Chalmers and O Farrel 1913 and in the nigra variety with a black pigment producing coccus *Micrococcus* (*Nigrococcus*) *nigrescens* Castellani 1911

The fungus appears as a mass on the hair shaft and embedded in a mucilaginous or gelatinous material It is particularly evident in moist regions The fungus consists of gram positive bacillary forms 4 to 10 microns in length and 0 3 to 0 6 micron in diameter which are straight somewhat curved and occasionally branching

The chromogenic bacteria are non motile gram positive and occur in clumps *A tenuis* produces small translucent colonies on sugar media The cocci produce either black colonies (*M nigrescens*) or yellowish red to red colonies (*M castellanii*) Ping Ting Huang (1933) isolated *Actinomyces sendaiensis* from 25 cases of lepothrix The fungus showed coccoid forms clubs and fila

diameter and many multilocular thick walled larger cells There are no asci Large numbers of a large *Staphylococcus* are often associated with the fungus, living perhaps in the mucoid material which is a by product of the growth processes of the fungus

Culturally the fungus grows as a yellowish rugose colony somewhat moist dull and irregular in appearance

EPIDEMIOLOGY AND GEOGRAPHICAL DISTRIBUTION

Piedra occurs in epidemic form in Colombia Brazil and British Guiana In Colombia the disease is attributed to the fact that women wash their hair with a mucilaginous oil In Brazil it is seen chiefly in students who use an oil from the cactus to smooth down their hair In British Guiana the natives believe it to be due to the use of white or milky water the disease is not found in those using the brown peat bush water

The disease is fairly widespread throughout the tropical countries and in Europe but may be found in the temperate zones

PATHOLOGY

The organism grows and surrounds the hair with a mucilaginous substance prevalent throughout the nodule and it may grow under the cuticular layer causing the hair to become weakened and brittle

SYMPTOMATOLOGY

The hairs of the scalp beard mustache axilla or groin are affected with the production of nodular gritty hard dark or light masses varying in size from a pin point to a pin head These are found in both males and females of all races particularly in Colombia Brazil and in other South American countries There may be many nodes on a hair shaft they may envelop it completely or grow only on one side They are usually found on the surface but may penetrate into the hair raising the cuticular layer rendering the hair brittle A crackling noise is heard when a comb is passed through a group of affected hairs

P hortai produces gray brown or black hard nodules *T giganteum* (*Piedraia colombiana* of Dodge) the type found in Colombia produces grayish white cream or light brown nodules which are somewhat softer translucent and enveloped with a mucoid substance

DIAGNOSIS

The characteristic nodules both macroscopically and microscopically are diagnostic per se

Almeida differentiates piedra into the white variety and the black type *white European piedra* (piedra nostras) producing nodules on the mustache rarely the beard produced by *Trichosporum beigelii* *T ovoides* and *T ovale* *white Japanese piedra* similar to *piedra* in Europe and caused by species of *Trichosporum* *white piedra of the New World* (Colombia Brazil—Rio de Janeiro and São Paulo) caused by species of *Trichosporum* *American black*

alcoholic solution of bichloride of mercury (1 1000) Other remedies have also been tried successfully These include sulfur and salicylic acid in an ointment such as Schalek s paste

℞	Phenol	0 3 gm
	Precipitated sulfur	2 0 gm.
	Salicylic acid	2 0 gm
	Zinc oxide	8 0 gm
	Starch	8 0 gm
	Vaseline to	30 0 gm
Sig	Apply to affected parts	

This ointment must be washed off frequently to avoid furunculosis However it is usually best to shave off affected hairs and apply fungicide locally

SEBORRHEIC DERMATITIS

Seborrheic dermatitis [seborrheic eczema or eczema seborrheicum (Unna) seborrhea seborrhea corporis (Duhring) seborrhea eczemaformis (Crocker) pityriasis simplex capitis seborrhea oleosa and seborrhea sicca (Hebra) pityriasis oleosa pityriasis steatoides (Sabouraud) pityriasis circinata and others] is an acute or subacute inflammatory dermatosis which usually begins on the scalp and is characterized in its final stage by the occurrence of rounded irregular or circinate lesions covered with yellowish greasy scales Associated with this disease is a yeastlike organism known as *Pityrosporum ovale*

ETIOLOGY

The fundamental lesion of seborrheic dermatitis (Fig 72) can be considered to be an infection with an organism There are a number of microbes which may be isolated from these lesions they include *Pityrosporum ovale Staphylo coccus albus* or *S epidermidis* streptococci and yeastlike fungi Because of the constant presence of *P ovale* in the lesions the increase in numbers of cells proportionate to the severity of the infection the spread of the organism in accordance with the spread of the lesions and the experimental production of lesions with an organism identified as *P ovale* this fungus is credited with playing an important role in seborrheic dermatitis There are however pre disposing factors which make it possible for *P ovale* an opportunist to produce the scaling and erythema that characterize the disease Of these the sebor rheic state or oily condition of the skin is most important in producing a satisfactory medium for the growth of the fungus Because of its morphology *P ovale* has been termed the bottle bacillus or balloon bacillus

As a result of intensive and extensive studies carried on over a period of years Sabouraud found the following organisms in the various types of sebor rheic conditions

ments Pure cultures were black Small isolated or confluent masses or nodes with a gelatinous sheath gray to yellow in color were produced experimentally on living attached hairs

EPIDEMIOLOGY AND GEOGRAPHICAL DISTRIBUTION

The infection is apparently spread from man to man and may occur in epidemic form Kneedler (1939) reported the disease as occurring in about one third of the scalps of school children in Siam but not in adults The disease is found chiefly in the tropics although it may be seen in the temperate zone The *flava* variety is practically universal The *rubra* type is next in incidence occurring chiefly in the tropics with some isolated cases in the temperate regions The *nigra* variety is next in incidence in the tropics with rare cases found in colder regions

PATHOLOGY

In the early stages of the infection the fungus may grow inward toward the cortex of the hair and consequently raise the cuticular scales and superficial fibers causing the hair to become brittle fissured and broken The direction of growth of the fungus however tends to be mainly outward to form the masses Usually when invasion is lacking the fungus occurs in masses embedded in the gelatinous matrix There may be an accompanying hyperidrosis with erythema of the adjacent skin

SYMPTOMATOLOGY

Trichomycosis axillaris is a nodular disease of the hair manifesting itself as nodes or diffuse masses either singly or multiple with many around the shaft The nodule may be soft or hard resembling at times piedra The sites of election are usually the axillae and the inguinal region but the scalp is rarely involved The skin in the axillae may sometimes be affected and present a lesion similar to erythrasma Aside from its aesthetic significance and a complaint of pseudochromidrosis (red sweat due to pigment of red cocci) trichomycosis axillaris is not serious but it may be persistent and chronic

DIAGNOSIS

The diagnosis is easily established microscopically by mounting the hairs in 20 to 30 per cent potassium hydroxide and discovering under high dry or oil immersion lens first the bacillary form of *A tenuis* and secondly the groups of cocci in the rubra or nigra varieties The color of the nodule is important in the final diagnosis The disease should be easily differentiated from piedra or trichosporosis

PROGNOSIS AND TREATMENT

Unless treated properly the disease tends to recur It is advisable to sponge the infected hairs with benzene and to follow this with an application of an

All of the cells described may be seen in the various stages of seborrheic dermatitis but whether they are all variants of the same organism or different species or genera has been a matter of dispute Certainly some of these cells may belong to the Cryptococci while others may be large Staphylococci

Moore described an organism cultivated on wort agar which measured from 2 to 11 microns The colonies developed first as grayish white growths which became ochraceous salmon to pinkish buff on different media Penham isolated strains on wort agar which were small budding orange brown in color Subcultures were obtained on agar plus an extract of various fats and fatty acids The colonies were small Emmons obtained primary cultures on a 28 per cent glycerin dextrose broth His strain grew poorly on ordinary media but showed lipophylic tendencies

EPIDEMIOLOGY AND GEOGRAPHICAL DISTRIBUTION

Seborrheic dermatitis in its various stages is universal The disease is infectious and easily spread from person to person The use of contaminated combs and brushes perhaps helps to spread the disease The finding of the organisms in a large percentage of cases suggests that the organism is an opportunist taking advantage of lowered resistance and other debilitating features on a substratum beneficial to the growth of the organism Age or sex play no part in hindering the susceptibility of the individual

PATHOLOGY

Seborrheic dermatitis in the simplest form pityriasis (simplex) Capitis consists of an exfoliation or desquamation of the horny layer of the epidermis in the form of small grayish white scales These scales become yellowish and greasy to the touch As the disease progresses inflammation accompanied by itching is seen When the disease starts to spread as a result of a seborrheic (oily) state and increase in the number of organisms there may be a secondary invasion by staphylococci streptococci and perhaps other yeastlike fungi to produce vesicles pustules oozing and crusting with the formation of large lesions and greater amounts of scaling

Microscopically the picture of seborrheic dermatitis in all its stages is essentially the same There is hypertrophy of the horny layer parakeratosis intercellular and intracellular edema in rete malpighii accompanied by acanthosis and inflammatory cellular infiltrate The lymph spaces in the upper part of the cutis are dilated The epithelium shows thickening with edema in the papillae The midcorium is infiltrated with lymphocytes and leukocytes The prickle cell layer papillae oil glands and ducts show an excessive amount of fat *The collagen is swollen The interpapillary rete pegs show flattening in* some places and lengthening and plugging in others Microscopic vesicles are present and the granular layer in some places appears to be lifted up by fluid *P ovale* can be seen in the lamellar interspaces and deep in the follicles affecting the hair

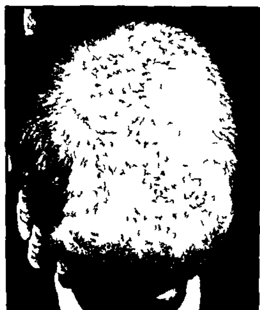



FIG 2 A Seborrheic dermatitis of scalp B *Pityrosporum ovale* in scrapings of seborrheic dermatitis

Pityriasis (simplex) capitis	Many *P ovale*
Pityriasis (simplex) sicca	*P ovale* present with or without *Staphylococcus albus*
Seborrhea oleosa	*P ovale* and staphylococci present with a microbacillus if hair is falling out and without if hair is healthy (The microbacillus is probably *Corynebacterium acnes*)
Pityriasis circinata	*P ovale* is usually present and loss of hair is not a feature

An examination of scrapings from the scalp and from lesions on the chest reveal numerous types and sizes of cells Malassez found large budding cells 4 to 5 microns in diameter small budding cells 2 to 2 5 microns in diameter and cells smaller than 2 microns without buds Bizzozero saw cells 3 3 to 3 5 microns in long axis and 2 3 to 2 6 microns in width Acton and Panja designated four forms a large swollen form 8 to 12 microns in diameter seen in quiescent lesions a flask form budding and regularly staining seen in the active disease small cocci seen also when the lesion is acute and spreading 2 to 3 microns and mycelial forms 2 to 3 by 15 to 20 microns seen in the stage of acute dry pityriasis particularly dandruff of the scalp Benedek found spherical banana shaped flask shaped and spherical budding forms

DIAGNOSIS

Seborrheic dermatitis in most of its phases is usually not difficult to diagnose However it is good to bear in mind such conditions as early psoriasis which may involve the scalp dermatitis venenata in rare instances pityriasis rosea and other fungous infections Streptococci and staphylococci may complicate the picture of seborrheic dermatitis especially in the axillae and behind the ears

On the seborrheic areas of the body seborrheic dermatitis exhibits circinate or oval lesions which are superficial never showing scarring or pigmentary changes In psoriasis the scales are markedly heaped up silvery imbricated and usually involve the elbows knees nails and extensor surfaces Pityriasis rosea has an acute onset is absent from the scalp and has a self limited course Dermatitis venenata is accompanied by intense itching a burning sensation and is limited to points of contact with the irritant Ringworm of the body found chiefly in children shows a raised inflammatory periphery may show scarring but usually shows papules and a tendency to start from the hands or feet

PROGNOSIS AND TREATMENT

In mild cases seborrheic dermatitis usually responds to treatment In untreated cases it may become widespread and severe with superimposed infections which are difficult to treat The disease is apt to show relapses recurrences and reinfections

Treatment consists of cleanliness and applications of medications suitable for the state in which the disease appears

For excessive oiliness of the scalp shampoos with tincture green soap once or twice weekly are recommended

Local application of antiseptics (with resorcin sulfur or thymol etc) has given good results

℞	Corrosive sublimate (bichloride of mercury)	0 18 gm
	Resorcin or resorcin monoacetate	9 00 gm
	Spirits of formic acid	15 00 gm
	Menthol	0 45 gm
	Oleo ricini	4 00 gm
	Alcohol (70%) q s ad	180 00 gm

Sig Apply three to four times weekly Shampoo once a week

If the patient is blond or gray resorcin monoacetate should be substituted for resorcin since resorcin tends to discolor blond hair

A good general antiseptic is *Liquor antisepticus N F* whose principal germicidal ingredient is thymol

For general seborrheic dermatitis of the scalp especially if there is a great deal of inflammation a sulfur ointment is usually to be recommended The

SYMPTOMATOLOGY

To understand seborrheic dermatitis two things have to be considered First that there is a condition known as seborrhea which is not a genuine disease but is a state of excessive oiliness of the skin which seems to be a hereditary or secondary sexual characteristic Secondly a group of lesions develop which are inflammatory in character and produced by certain micro-organisms on a seborrheic base The picture may then become complicated by secondary invaders such as staphylococci and streptococci The first stage is known as *pityriasis simplex pityriasis simplex capitis seborrhea sicca* or *pityriasis sicca* This is a desquamative state which manifests itself by the formation of dry branny scales which are small and somewhat brown to gray in color In this stage *Pityrosporum ovale* is found in fairly large numbers The hairs are dry and lusterless and there is some itching Inflammation although present may not always be obvious Hair loss may be present

The *sicca* stage then gives way to the second stage known as *pityriasis steatoides* or *pityriasis simplex oleosa* The dry scales become waxy or greasy in appearance The underlying skin becomes reddish and inflamed and the scales become much coarser yellowish waxy and more loosely adherent There is increased itching As a result of the acute or subacute inflammation serum is produced which gives the scales a sticky appearance with the consequent production of crusts in moderate amounts The lesions become widespread on the scalp and form an inflamed region which at the hairline form the clinical entity known as corona seborrheica or seborrheic crown of Unna A secondary infection with staphylococci accentuates the sticky appearance and crust formation to produce what is referred to as *eczema capitis P ovale* is found in abundance as well as myriads of *Staphylococcus albus* Spores of contaminating fungi such as *Aspergillus* or *Penicillium* may be found occasionally

If left unchecked the disease progresses to the final stage of *seborrheic dermatitis pityriasis circinata* and as a result of secondary bacterial involvement forms the oozing or weeping *seborrheic eczema* of Unna The disease may spread from the scalp to the forehead to the postauricular region and the axilla where staphylococci and streptococci play a major role The eyebrows and eyelids become involved with severe itching to form the entity *blepharitis marginalis* The spread continues to the nasolabial folds or the butterfly region of the face The spread if not checked continues to the presternal and interscapular regions to produce reddish circinate plaques covered with yellowish greasy scales and is called *pityriasis* or *seborrhea corporis* of Duhring Here the lesions may remain in a recurrent state for years presenting severe exacerbations and intense itching Occasionally the lesions may become widespread over the body These lesions have been termed seborrheids and are attributed to a lesion of seborrheic dermatitis elsewhere on the body usually the scalp *P ovale* may be found in large numbers but *S albus* may also be found as well as other organisms

CHAPTER LVI

DERMATOMYCOSES

MORRIS MOORE

MICROSPOROSIS

MICROSPOROSIS IS A DISEASE OF THE SCALP AND SMOOTH skin of children and of the beard rarely of the scalp and of the skin in adults referred to also as ringworm tinea tinea circinata The organisms are found in two groups microspora of human origin transmitted from man to man typified by *Microsporum audouini* Gruby 1843 and the other microspora of animal origin transmitted from animal to animal or animal to man and typified by *M canis* Bodin 1902

ETIOLOGY

Microsporum audouini the type species of the genus *Microsporum* was first described and named by Gruby in 1843 on the basis of the size and appearance of the mycelial spores seen on the hair shaft Subsequently it has been cultured on numerous occasions and given a definite morphologic description especially by Sabouraud

When an infected hair (in 20 to 30 per cent potassium hydroxide) is examined microscopically there are seen layers of fungus spores approximately 2 to 3 microns in diameter closely compact somewhat with the appearance of a mosaic. They extend down the hair into the follicle forming a fringe at the base just around the bulb known as Adamson s fringe The fungus grows first as a filamentous organism approximately 2 to 3 microns in diameter particularly as seen at the mouth of the hair follicle The mycelial structures grow down and into the follicle and come to rest on the hair shaft The fungus (Fig 73) then invades the hair cuticle and extends up the hair forming fine filaments or chains of cells which result from the breaking up of the hyphae The growth of the organism in the hair cuticle and on the outside of the hair shaft causes the hair to become brittle and break off

In the glabrous skin or around the mouths of hair follicles the fungus consists of a branching intertwining network of septate mycelial elements about 2 to 4 microns in diameter These may eventually break up into arthrosporous-like cells about 3 microns in diameter arranged in small groups The micro-

amount of salicyclic acid added depends on the amount of inflammation The following prescription has proved beneficial

℞	Precipitated sulfur	6 00 gm
	Salicylic acid	3 00 gm
	Vaseline	60 00 gm
Sig	Shampoo the scalp thoroughly and then apply the ointment daily for a week then shampoo again	

This ointment may also be used for lesions on chest

It is important not to use hot irons on the hair when using sulfur or mercurial preparations since the hot iron produces chemical changes in these drugs causing the hair to become discolored

animal types are *M canis* vel *lanosum* Bodin 1897 Sabouraud 1907 should be *M canis* Bodin 190 *M felineum* Fox and Blaxall 1896 *M fulvum* Uri buru 1907 (usually quoted as 1909) *M villosum* Minne 1908 *M pubescens* Sabouraud 1909 and *M tomentosum* Pelagatti 1919

EPIDEMIOLOGY AND GEOGRAPHICAL DISTRIBUTION

Microsporosis is highly contagious Epidemics have been known to occur in families among school children and in institutions of various kinds includ ing foundling homes The disease occurs as tinea capitis chiefly in children although adults may occasionally be affected It seems to be endemic in cer tain countries and is prevalent throughout the entire world In northern Europe and in England the chief species seems to be *M audouini* but it is uncommon in southern Europe and in the tropics except for Brazil and a few other countries *M audouini* seems to cause the greater number of lesions in the eastern part of the United States while *M canis* is more prevalent in the midwest and western region of the United States and in the tropics *M fulvum* first isolated in Argentina has induced a few cases throughout the United States

PATHOLOGY

Growing as they do in the stratum corneum and extending somewhat into the dermis the fungi usually cause erythema or edema similar to that found in any inflammation of the skin There is hyperplasia of the cells of the epi dermis and cutis dilatation of the vessels of the papillary layer with infiltra tion of plasma and multinucleated cells presenting often a granulomatous picture There may be parakeratosis of the stratum corneum acanthosis hyper keratosis and interstitial edema The inflammation causes a scaling of the stratum corneum and vesicle formation

SYMPTOMATOLOGY

Lesions produced by human microspora such as by *M audouini* are formed chiefly on the scalp—tinea capitis or tinea tonsurans—and may occur as faint circinate lesions on the nape of the neck of children Adults are rarely affected by this organism

On the scalp the lesions usually begin insidiously have mild symptoms and show little inflammation but they are chronic and resistant to treatment The temporal and occipital regions are favorite sites for the fungus with the lesion spreading peripherally but rarely affecting other parts of the body On the scalp however areas of nearly complete alopecia are found which are sharply marginated and usually circular Within these patches can be seen the short broken off stumps of hair extending for a short distance above the surface of the scalp (2 to 4 mm) These stumps can be pulled out very easily and show a frosted coating which consists of the fungus spores Where desquamation has taken place as a result of edema and dryness due to the presence of the fungi the plaques in the scalp show a certain degree of scaliness with dry

scopic picture is alike for both the human and animal *Microsporum* except that there is a greater abundance of the fungus in the latter

In culture *M audouini* develops a growth which appears at first like a



Fig 45 Hair infected with *Microsporum canis* Note small spores

dandelion seed then it shows a central cottony elevation grayish white in color which becomes buff with age There is little aerial mycelium The colony develops as a circular growth with a slightly fringed periphery and a few radial grooves extending from the raised central button to the edge of the growth Pleomorphism is rare

The animal microspora exemplified by *M canis* appear very rapidly as a fluffy growth The central area of the colony soon becomes somewhat powdery and this is surrounded by a cottony growth (concentric formation) Grooves may be radial but are usually concentric The color of the colony becomes buff to tan and pleomorphism develops in approximately four to five weeks as cottony outgrowths A yellow pigment is developed on the under surface which diffuses into the substratum This is a characteristic of *M canis*

Microscopically all of the microspora show the characteristic macrospores or fuseaux chlamydospores microspores or aleurospores racquette mycelium nodular organs pectinate bodies spirals and conidia These structures are lessened in number in the human group especially the fuseaux

On the basis of gross cultural characteristics Sabouraud lists the following human and animal types of *Microspora* Human forms are *M audouini* Gruby 1843 *M velveticum* Sabouraud 1907 *M umbonatum* Sabouraud 1907 *M tardum* Sabouraud 1909 *M equinum* (Delacroix and Gueguen) Bodin 1904 is cited as a form intermediary to human and animal types The

The animal microspora usually produce lesions which are of short duration (approximately three months) and which may involute spontaneously

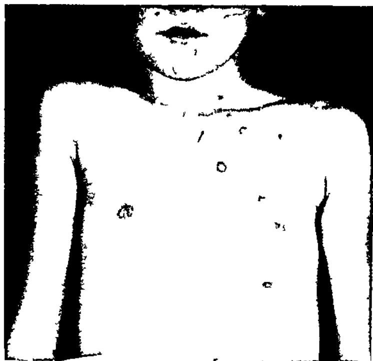


FIG 75 Tinea circinata caused by *Microsporum canis*

DIAGNOSIS

Microsporosis can usually be diagnosed without resort to laboratory methods if the clinician examines the lesion with a hand lens The presence of the short broken hairs in the lesion is important However if the stumps of hairs which may be pulled out with care are mounted in potassium hydroxide the characteristic frosted appearance will establish a diagnosis Diagnosis can also be made with the aid of the Wood light The latter consists of ultraviolet light with wavelengths in the region of 3 659 angstrom units which gives the best fluorescent value Lewis and Hopper advise the glass filter (Corning glass violet ultra number 586) polished to a thickness of from 4 to 5 mm The glass contains sodium barium silicate with somewhat less than 9 per cent nickel In a dark room infected hairs exposed to this light show a brilliant fluorescence It is necessary to cultivate the infected hairs to determine the species of fungus present This is important for the further treatment of the infection

grayish scales which give the disease the name gray patch Occasionally considerable amounts of inflammation may cause confusion between human and animal microsporosis



Fig 74 A Microsporosis of scalp B Gray patch of microsporosis

In children the animal microspora are the frequent cause of tinea capitis (Fig 74) and of tinea glabrosa (tinea of the glabrous skin) In adults these organisms especially *M canis* produce lesions of the smooth skin and of the beard Kerion lesions of the scalp usually reported as due to *Ectotrichophyton* can be caused as well by animal microspora *M canis* and *M fulvum* have been isolated from these lesions which are highly inflamed oozing tender boggy enlargements which when incised show no pus but a small amount of serous fluid In general *M canis* produces lesions which closely resemble those caused by *M audouini* but which may be somewhat more inflamed Lesions of the smooth skin differ somewhat from those of the scalp in that they show scaliness with hyperkeratotic raised borders no definite vesicle formation and are round or oval

Lesions of microsporosis (Fig 75) may give rise to the microsporid a papular or even vesicular discrete or confluent localized or generalized eruption due to either an allergy to the fungus which is present in a primary focus of infection or perhaps to the dissemination of the fungi themselves by way of the blood stream Fungi cannot be demonstrated in these lesions and consequently the general opinion is that the lesion is the result of sensitivity to the fungous products Treatment of the primary focus will clear up the microsporid

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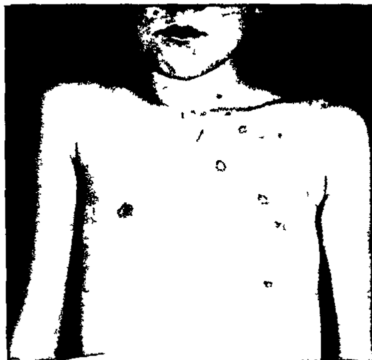


Fig 7 Tinea circinata caused by Microsporum can

DIAGNOSIS

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PROGNOSIS AND TREATMENT

The prognosis in the case of the animal microspora is very good These lesions are usually of short duration six weeks to three months they tend to clear up spontaneously and usually disappear at puberty Human microsporosis on the other hand has not as good a prognosis The lesions do not heal spontaneously and if left unchecked will persist for months or years They are resistant to treatment and tend to spread involving the scalp with large plaques and smaller satellite lesions

In non resistant microsporosis a topical application of an ointment made up with 3 per cent salicylic acid and 5 per cent ammoniated mercury or a mild sulfur compound ointment (3 per cent salicylic acid and 3 to 5 per cent sulfur) rubbed into the affected area twice daily offers a mild but effective treatment High concentrations of sulfur and ammoniated mercury should be avoided in this type of the disease The resistant type of infection however presents a problem One of the methods used is to epilate the infected hairs This can be done manually by thallium salts or by roentgen rays Manual epilation is tedious and not always practicable This is done usually in small patches at three to four day intervals A 10 per cent ammoniated mercury ointment is applied to the scalp to prevent further spread of the infection Epilation by thallium salts is a dangerous procedure and we do not feel that its use is warranted Roentgen ray epilation may be used but only by one trained in its administration since permanent alopecia may result if it is misused A mild ointment of 3 per cent ammoniated mercury should be applied to the scalp following completion of roentgen administration

TRICHOPHYTOSIS

The Trichophyta like the Microspora produce ringworm of the scalp glabrous skin and beard but in addition a number of other clinical pictures *seen in the nails hair inguinal region toes interdigital spaces* axillae and the body in general Each lesion varies according to the site and to the organism responsible Accordingly in the scalp the following are produced tinea capitis (tinea tonsurans black dot ringworm) kerion Celsi and suppurative tinea or agminate folliculitis On the glabrous skin the lesions are tinea circinata (tinea corporis trichophytosis corporis tinea glabrosa) and granuloma trichophyticum or Majocchian granuloma On the nails trichophytosis appears as tinea unguium and leukonychia trichophytica The beard gives rise to lesions called sycosis barbae or tinea barbae Trichophytosis is caused by members of the family Trichophytoneae of the Fungi Imperfecti including such genera as *Trichophyton Megatrichophyton Ectotrichophyton* and *Favotrichophyton*

ETIOLOGY

The organisms responsible for trichophytosis have perhaps been the most discussed group of microbes of all the pathogenic fungi The most valuable

work on the classification and differentiation of the organisms referred to as dermatophytes is that of Sabouraud (Les Teignes) His system is based on the habitat Thus the *Trichophytons* are those organisms that affect hair the *Epidermophytons* are those that do not attack the hair and the genus *Achorion* is described as the causative agent of the disease favus This system of course is not perfect since it does not consider completely the botanical affinities of each organism However for the clinician it presents a workable basis for determination of the organisms and as such is considered here with due respect to mycologic classifications of others For a complete discussion of the organisms the reader is referred to Dodge Emmons Castellani and Chalmers and Gregory

Sabouraud classified the *Trichophytons* primarily on the appearance and location of the organism with respect to the hairs involved

I *Trichophyton endothrix* The fungous elements are found within the hair substance

II *Trichophyton neo endothrix* The organism is found chiefly within the hair shaft with a few filaments present on the surface of the hair

III *Trichophyton ectothrix* The fungus grows and reproduces on the surface of the hair but may also invade the hair substance This has two main groups

A The microid or small spored group

1 The gypseum group characterized by powdery cultures

2 The niveum group having a snow like colony

B The megalospore or large spored group

1 Downy group with velvety cultures

2 Faviform group with smooth cultures

The family Trichophytoneae includes the whole group of dermatophytes comprising *Microsporum* already described *Epidermophyton* *Endodermophyton* and *Achorion* to be considered later and the heterogeneous group of *Trichophyton* which is now under discussion The number of species isolated in temperate zones and in the tropics is far too large to be considered individually Consequently only the Trichophytons representing the type species will be briefly described since all other species vary from these merely in color gross appearance of colony or measurement of the characteristic organs-spores and so forth

In general the Trichophytons have a white mycelium with various species having a yellow brown pink red or violet color They reproduce by various types of cells including arthrospores microspores or aleurospores conidia chlamydospores and macrospores (fuseaux) which are clavate multicelled and may often be lacking in culture

Trichophyton endothrix

Type species *Trichophyton tonsurans* Malmsten 1845

The organism is found within the hair substance as chains of spherical to cuboidal spores 5 to 6 microns in diameter It produces ringworm of the

scalp rarely of the glabrous skin and of the beard which resembles microsporon infection Microscopically cultures of this organism exhibit microspores both lateral on the hyphae and on short pedicles (thyrses) showing transitional forms to small chlamydospores Hyphal tips are clavate The culture is white velvety and crateriform with a central button The growth becomes powdery with a yellowish color It usually shows immersed rays with age

Trichophyton violaceum Sabouraud apud Bodin 1902 or *Favotrichophyton violaceum* (Sabouraud ap Bodin) Dodge 1935 is one of the endothrix types which affects the scalp producing tinea tonsurans with many scattered patches The infected hairs are broken off close to the scalp producing the black dot ringworm It affects also the nails beard and glabrous skin The organisms in culture produce a rich violet color The surface is shiny showing several radial folds Growth of the fungus is definitely slow about half as fast as that of *Trichophyton tonsurans* Pleomorphism is present A variety of this fungus var *Khartoumense* (Chalmers and MacDonald 1915) produced tinea capitis in a Sudanese school girl

Trichophyton neo endothrix

Type species *Trichophyton flavum* Bodin 1902

The elements of this organism also known as *T cerebriforme* are found essentially within the hair shaft but some filaments occur on the surface of the hair The lesions are characterized by small follicular abscesses affecting the scalp beard and body The fungus is seen in the form of branching chains of cuboidal cells in and on the hair 5 to 6 microns in diameter When cultivated the colonies have a cerebriform or folded surface The color is at first white then cream and finally yellow in the center The growth then becomes crackled with unequal ray formation Microscopically the organisms show many chlamydospores lateral aleurospores and an abundance of arthrospores

Trichophyton ectothrix

Type species *Ectotrichophyton mentagrophytes* (Robin) Castellani and Chalmers 1919

This organism the type species of the microid or small spored gypseum group is seen on the outside of the hair shaft as filaments and chains of small spores (Fig 76) 3 to 4 microns in diameter It is described in the literature by many as *Trichophyton gypseum* Bodin 1902 But there is now no doubt that it is synonymous with *E mentagraphytes* It is the chief cause of kerion of the scalp and the beard although kerion may be produced by species of *Microsporum* and by other *Trichophytons* Lesions are produced on the scalp hair glabrous skin including the face trunk arms and hands legs and feet and also the nails They appear as areas or plaques which are oval circular or irregular with scaling vesiculation pustule or papule formation There is hyperkeratosis with or without maceration crusting or fissuring On the hands and feet are found lesions of an eczematoid nature with vesicles and pustules

E mentagrophytes grows fairly rapidly in culture producing a powdery disc with a central knob and cut by deep furrows On Sabouraud s glucose agar the colony shows powdery rays which become lanceolate Pleomorphism

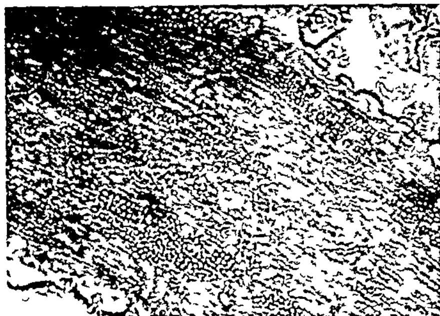


Fig 76 Hair infected with *Ectotrichophyton*

takes place in from four to five weeks The reverse of the colony is reddish The pleomorphic colony shows a velvety appearance with usually an umbilicate center Subcultures of the pleomorphic mycelium usually result in completely pleomorphic colonies with a sterile mycelium

Microscopically the colony exhibits a few chlamydospores and numerous aleurospores borne in clusters (grappes) and in compound thyrses Many spirals are present as well as two or three celled macrospores

Trichophyton gypseum is described in the literature as having four different types of growth (1) white fluffy growth which becomes velvety and buff colored (2) *a granular variety with a powdery surface light buff to yellow* in color the whole becoming pleomorphic (3) a downy growth developing into a fluffy mass rapidly covering the agar surface—the *T interdigitale* type (4) the *T niveum* type starting as a white and fluffy growth which becomes compact with surface ridging

These four types differ somewhat microscopically hence it may be that they are not related

In the niveum group the type species is *Ectotrichophyton felineum* (Blanchard) Castellani and Chalmers 1919 This organism was named *Trichophyton*

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above the surface of the skin The stumps can be easily pulled out showing a swollen condition due to the invasion by the fungi The surrounding cutaneous surface shows a reddening and some inflammation and may be thickened with



Fig 77 Kerion of the scalp

superficial scaling The histopathologic picture is similar to that seen in microsporosis exhibiting noticeable edema parakeratosis of the upper layer of the skin vascular dilatation round cell infiltrate into the upper cutis acanthosis which may be mild or accentuated hyperkeratosis leukocytic infiltrate in some cases especially where there are pustules to be found in advanced cases and an interstitial edema Vesicle formation is usually absent

As the disease advances there is an intermediary form where the lesions exhibit more inflammation and reddening The follicular openings may become wider and may exude pus or a seropurulent material particularly apparent in sycosis barbae

The second or deep type of lesion is characterized by the suppurative tinea or kerion and agminate folliculitis already described for *Microsporum canis* and a third lesion known as *granuloma trichophyticum* or *Majocchian granuloma* These are granulomatous lesions indurated brightly inflamed chronic and fairly resistant to treatment These characteristics are particularly evident in kerions and somewhat modified in others The kerions (Fig 77) show a reddish to purplish surface with numerous small pustules The underlying

felineum by Blanchard and was later named *T radians* Sabouraud 1910 as characteristic of the *T niveum* group

The organism produces vesicular inflammatory lesions of the glabrous skin and kerion formation In culture it produces a velvety colony with a crateriform center snow white in color It shows no pleomorphism It has been suggested as a pleomorphic form of the gypseum group

The ectothrix megalospore (large spored) group is represented by *Megatrichophyton roseum* (Bodin) Dodge 1935 This organism is also known as *Trichophyton roseum* Bodin 1902 *T rosaceum* Sabouraud 1919 and *Megatrichophyton megnini* Neveu Lemaire 1921

This fungus produces a network of mycelium on the surface of the hair made up of chains of large spores 6 to 8 microns in diameter It produces lesions of the smooth skin beard and nails with little or no inflammation

In culture *M roseum* starts as a velvety white colony which becomes pale rose and the reverse gooseberry violet The colony is divided into raised sectors Pleomorphism starts at the margin of the colony as a white growth and the surface shows narrow radial folds

In the faviform group the type species is *Favotrichophyton ochraceum* (Sabouraud) Neveu Lemaire 1921 also known as *Trichophyton ochraceum* Sabouraud 1908

This organism produced impetiginous lesions of the smooth skin of the body and kerion of the beard

The colony begins as a small ochre yellow protuberance with a sulfur yellow border It becomes somewhat cerebriform with age Microscopically it shows mycelium and chlamydospores only

EPIDEMIOLOGY AND GEOGRAPHICAL DISTRIBUTION

The Trichophyta are capable of inducing epidemics either as tinea capitis or ringworm of the body in children particularly among school children In adults these organisms can spread from man to man producing lesions on the beard The occurrence of lesions in members of the same family points to an ability of the fungi to spread easily The organism may be disseminated by transmission from person to person or from animal to person Horses cattle dogs and cats may be carriers of the organisms

The Trichophyta are widespread throughout the world both in temperate and tropical regions and have been reported in both sporadic and epidemic form Some show a tendency toward endemicity but no one seems to be immune Although a great number of cases have been reported from Europe many species have also been isolated in South America North America Africa Asia and the tropical islands Some species are more common in some areas while rare or absent in others

PATHOLOGY

In general there are two types of pathologic lesions The first or superficial involves the hairs and the superficial portion of the skin The infected hairs become brittle dry and harsh and break off easily a few millimeters

to infection of the feet The id may be generalized but disappears when the original focus of infection is adequately treated

Pustular dermatophytosis generally found on the backs of the hands devel

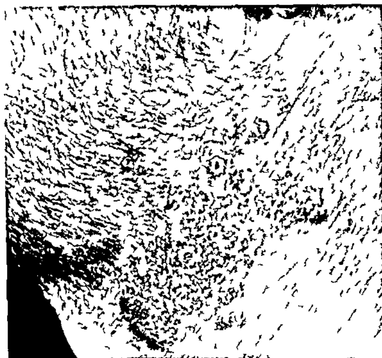


Fig 8 Tinea barbae

ops as a folliculitis involving the subcutaneous tissue to form granuloma When the deeper tissues are involved the resultant lesion is the granuloma of Majocchi

Due to a continued irritation the hyperkeratotic lesion is formed especially on the heels and soles

Lesions of the nail may be caused by species of *Trichophyton Epidermophyton Achorion* and *Monilia* The fungi live either superficially or deep in the nail tissue *When superficial the fungus produces opaque sharply outlined* patches *leukonychia trichophytica* When invasive the nail becomes dry lusterless thickened brittle and yellowish in color The disease spreads and the nails become thickened then somewhat scaly uneven dystrophic with ridges As a result of inflammation in the subungual tissue the nail may separate from the underlying structures The lesion may spread to the sides and webs of the fingers The nails usually serve as a source of infection for lesions elsewhere on the body

tissue is honeycombed and filled with a serous or purulent material The agminate folliculitis likewise shows pustules

The Majocchian granuloma usually caused by *T violaceum* differs in that the lesions are sharply defined with a smooth surface and may be hard They *may be chronic and resistant to treatment Histologically these granulomas* show acanthosis parakeratosis capillary dilatation and a perivascular infiltrate The cellular infiltrate becomes more intense in the deeper cutis The sharply defined granuloma simulates a tuberculous process with fibroblasts eosinophiles epithelioid and Langhans giant cells Many of the tubercles have a central area made up of leukocytes and eosinophiles (micro-abscesses)

When the nails are affected they become rough dry brittle ridged spongy and at times honeycombed Sharply defined opaque patches which are asbestos-like may be seen these are often called *leukonychia trichophytica*

SYMPTOMATOLOGY

In general the lesions may be seen as one or as a combination of two or more of the following clinical forms vesicular pustular macular scaling hyperkeratotic callous lichenified macerated or fissured

In the scalp *Trichophyton* produces tinea capitis or tinea *tonsurans* Tinea capitis is usually a disease of childhood but may be found occasionally in an adult Lesions of the scalp begin as small scaly patches These enlarge cause the hair to become brittle and break off to form a black dot type of ring worm The patches show inflammation vesicle formation and eventually patches of alopecia which when caused by *T violaceum* may be permanent areas of alopecia Secondary infection will change the original picture

Infections rarely may involve the eyelids to produce *folliculitis with severe* inflammation edema exudation little or no itching some scaling and loss of eyelashes

Lesions of the beard (Fig 78) result in discrete or confluent plaques of folliculitis with itching and pustule formation Deep inflammation may follow forming areas of alopecia as in the scalp Localized tumor like swellings may be formed which are single or multiple and deeply inflamed

Ringworm of the glabrous skin (Tinea glabrosa) is either papular hyperkeratotic pustular or commonly squamous It starts as a small scaly inflamed patch to form enlarged concentric discrete to confluent or arcuate patches which are reddish pinkish or brownish in color scaly irregular rounded or oval Itching or burning sensations may be present

Lesions of the hands and feet are vesicular consisting of groups of sago grain vesicles accompanied by intense itching occurring chiefly in hot weather The vesicles rupture then dry up to form macules or they become confluent to form bullae which may become secondarily infected Bullous lesions found between toes usually develop the macerated type of lesion with crusting fissuring or cracking which desquamates to leave large inflamed plaques without the horny layer

Trichophytids similar to microsporids are seen on the hands as vesicles due

Lesions of the beard are usually characteristic but should be differentiated from sycosis vulgaris which is a follicular pustular staphylococcus infection Kerion of the beard may simulate actinomycosis of the jaws or carbuncles

Glabrous skin lesions should at all times be diagnosed only after the fungus has been demonstrated Pityriasis rosea seborrheic dermatitis and psoriasis should be ruled out

Lesions of the hands and feet are often difficult to differentiate from bacterial infections staphylococcal and streptococcal dermatitis It is not always pos sible to demonstrate fungi in one attempt Where there is vesicle formation one should look for fungi in the fluid or in the roof of the vesicle Yeastlike organisms are found in the fluid but Trichophytons can be seen in the roofs of the vesicles Vesicle formation in fungous infections is usually peripheral while in bacterial infections they are usually in the center of the lesion often involving the whole patch In lesions of the feet one should be careful to dis tinguish the various artefacts including mosaic fungus or what has been determined to be cholesterol crystals

Nail lesions should be differentiated from psoriasis favus and vitamin de ficiency The finding of the characteristic fungi is important Usually vitamin deficiency psoriasis and favus produce lesions elsewhere on the body which should make it easy to arrive at a correct diagnosis

TREATMENT AND PROGNOSIS

The treatment of tinea depends on the organism causing the lesions There are perhaps more formulas for the treatment of tinea of the skin than for any other types of infections This is no doubt due to the resistance of the disease to treatment recurrence of the infection and spontaneous cure at times The preparation of autogenous vaccines in the treatment of fungous infections has been studied by many different investigators The results as far as treatment are concerned have been debatable and not very encouraging

Treatment is aimed particularly at the eradication of the fungus However caution must be exercised and due consideration given to the status of the lesion that is the amount of inflammation the possibility of secondary infec tion the intensity of the disease the duration of the lesion and the distribu tion of the infectious process but especially consideration of the etiologic agent Chemical methods may be of great value but intensive treatment of this type may irritate the skin to a point of chemical dermatitis Rather it is best to try to alter the host parasite relationship in favor of the host so that the fungus cannot live in the induced physiologic alteration

In treating tinea it is important that attempts should be made to keep the lesions clean from scaling and bacterial contamination Often a preliminary mild antiseptic should be used to rid the lesion of secondary infection The vesicles should always be opened aseptically so that the fungicidal agents may be able to penetrate The use of salves or ointments although of great bene fit in many diseases is not always satisfactory in vesicular eruptions Wet

Tinea of the inguinal region will be discussed under epidermophytosis

Tinea albigena which was first described by Nieuwenhuis in Java and confirmed by Jeanselme in observations made in Indo China and Siam was also found in the Malayan Archipelago and Ceylon It is an eruption affecting the palms and soles extending up the arms and legs and occasionally affecting the nails It is characterized by the formation of small itching nodules which develop into bullae The bullae rupture exuding a clear serum There is desquamation which leaves the skin tender and pruritic Marked hyperkeratosis develops with fissuring The skin becomes dry and keratinized Depigmentation follows leaving white patches or areas of leukoderma The disease is chronic occurring in young or old The etiologic agent is *Aleurisma albiciscans* (Nieuwenhuis) Dodge 1935 (*Trichophyton albiciscans*)

Tinea nigro circinata was observed by Castellani among Sinhalese natives The causative agent although not cultivated was named *Trichophyton ceylonense* Castellani 1908 It develops rings with thick elevated margins on the neck and scrotum The center is pinkish or covered by a dark crust while the periphery is elevated dark in color almost black No evidence of papules or vesicles The eruption usually disappears spontaneously

DIAGNOSIS

The diagnosis of the various lesions of trichophytosis depends largely on the location of the infectious process and the clinical features of the lesion However in all cases the nature of the infection should be definitely established by the finding of the fungus involved and by determining its genus and species Fungous vaccines may be tried for diagnostic purposes but the reactions vary so much with different individuals that they must be interpreted with caution Reactions to fungous extracts or to trichophytin microsporin oidiomycin or whatever the fungus used may be are of several types These may be urticarial the late tuberculoid inflammatory response to intradermal injection or eczematous when applied as patch tests Positive reactions do not necessarily imply that the present lesion is fungous in nature the patient may be sensitized to a former infection Negative reactions do not necessarily mean that the lesion is not fungous since it may be that the patient has not yet developed a sensitivity to the fungus

Lesions of the scalp should be differentiated from microsporosis favus and other fungous infections by finding the characteristic fungi in or on the hair Trichophytosis differs from microsporosis in that the lesions are circular irregular or oval and are usually associated with pustule formation vesiculation and scaliness The kerion is particularly characteristic of the *ectothrix Trichophyton* although it may also be produced by *M audouini* and *M fulvum*

The Wood light may be useful since in endothrix infections the hairs fluoresce dull and bluish while ectothrix usually does not fluoresce The disease should be further differentiated from seborrheic dermatitis and bacterial infections

Crude coal tar made up in 5 to 20 per cent strength in an ointment or paste and painted on full strength is helpful Ammoniated mercury 4 to 10 per cent in ointment or paste is highly fungicidal Schalek s paste likewise may be used as an antiparasiticide

In the case of nail infections where the nails have been cut or filed down the painting on of per cent iodine crystals in benzol is beneficial The use of 40 per cent salicylic acid plaster is also a satisfactory remedy

Roentgen rays have been used with some degree of success when the Kienbock Adamson technique is followed Epilation of hairs of infected regions such as the scalp and beard can be successfully carried out by a trained dermatologist Usually 300 r unfiltered radiation is sufficient to epilate the infected hairs

Tinea of the scalp can be treated by clipping the hair short washing the scalp with soap and water once daily and then applying an ointment consisting of 5 per cent salicylic acid and 10 per cent sulfur in vaseline If there is any reaction the treatment should be discontinued for a few days and then repeated

Tinea of the beard can be treated by epilation of the hairs if the lesion is localized followed by the application of 3 per cent salicylic acid and 5 per cent ammoniated mercury Cleanliness is an important part of the treatment Sulfur ointment 5 to 10 per cent may be applied daily but should be preceded by careful cleansing of the lesion

Tinea corporis can be treated by using one of the antiparasiticides such as ammoniated mercury ointment or Schalek s paste A sulfur ointment containing 5 to 10 per cent sulfur may be beneficial

Tinea of the hands or feet should be treated with care since lesions in these areas tend to relapse Treatment should be directed first at clearing the debris and ridding the lesions of the secondary pyogenic invaders Acute vesicular lesions can be treated by one of the methods described The feet can be soaked in 1 10 000 bichloride of mercury in lukewarm water two to four times daily for ten minute periods This should be watched carefully Potassium permanganate soaks are helpful In chronic infections the various antiparasiticides or keratolytic agents may be used to rid the lesions of the superficial layer of skin Daily washing is advocated as well as gentle rubbing to rid the lesion of the scaling skin As a prophylactic, dusting powder should be applied daily between the toes The following dusting powder advocated by Sutton and Sutton is helpful

℞	Camphor	ʒ ss
	Salicylic acid	gr X
	Zinc oxide	
	Cornstarch	
	Zinc stearate	āā ad ℥ i
Sig	Dust between toes and in shoes to keep feet dry	

Treatment of lesions of groin will be discussed under epidermophytosis

packs or soaks are preferable but they must be used with caution and discontinued if the skin shows any reaction to the chemicals in the preparations

In the treatment of tinea there are a number of factors which must be considered Tight clothing especially underwear or girdles keep the inguinal region moist warm and poorly ventilated and consequently make the treatment of lesions in this area difficult Tight shoes keep the toes in close proximity to each other and should therefore be avoided Stout people have a tendency to perspire freely and should keep their bodies dry

A number of chemical agents have been used in the treatment of tinea These have been fully described by Sutton and Sutton and by Wise and Sulzberger Some of these may be briefly noted

In acute inflammatory vesicular edematous or oozing conditions (1) wet dressings (2) lotions (3) pastes or (4) salves are advocated These consist of (1) boric acid (saturated solution) 2 per cent salicylic acid solutions silver nitrate 0 1 to 0 2 per cent (especially indicated for secondarily infected lesions) pure glycerin packs potassium permanganate 1 1000 or 1 5000 solutions or aluminum acetate 1 500 for wet packs (2) calamine lotion 15 to 20 per cent equal parts of zinc oxide talc glycerin and water and 0 5 per cent phenol (3) Lassar s paste with or without salicylic acid which is made up as follows

℞	Zinc oxide	25 00 per cent
	Cornstarch	25 00 per cent
	White vaseline	50 00 per cent

Lassar s paste with either ichthyol 3 to 10 per cent or crude coal tar 3 to 5 per cent (4) zinc oxide ointment (U S P) boric ointment (U S P)

For less inflamed lesions showing less exudation and not so acute Liquor carbonis detergens 4 to 20 per cent in shake lotion or ointments crude coal tar 0 5 to 10 per cent in ointments or pastes ammoniated mercury 2 to 10 per cent in ointments or pastes ichthyol 5 to 20 per cent in lotions ointments or pastes The addition of one of the following antipruritics is very beneficial phenol 1 per cent menthol 0 25 to 1 per cent ichthyol 3 to 10 per cent salicylic acid 1 to 2 per cent spirits of camphor 2 to 4 per cent

In chronic conditions or when the skin is particularly thickened keratolytics or strongly fungicidal agents are helpful The application of 10 per cent salicylic acid in alcohol induces scaling but should not be continued for more than a few days at a time Soap and water used with a scrubbing brush often is as good a means of débridement as any in chronic thickened lesions of the feet Whitfield s ointment is frequently used but must often be diluted with vaseline since it proves fairly strong

℞	*Salicylic acid*	*6 00 gm*
	Benzoic acid	12 00 gm
	White vaseline to make	100 00 gm

elongate Chlamydospores are present On repeated subculture the fuseaux become single celled and the arthrospores become rare Sabouraud reported that finally only aleurospores are produced

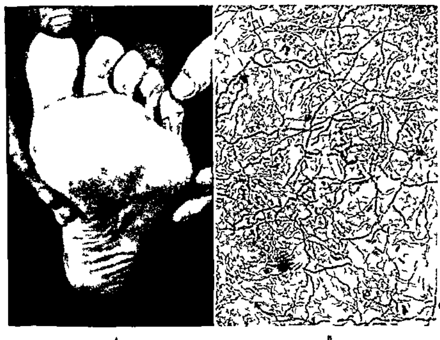


Fig. 79 A Epidermophytosis of foot caused by *Epidermophyton (Trichophyton) purpureum* Note fissuring B Scraping from epidermophytosis of toes Note interlacing network of filaments

E interdigitale grows more rapidly than does *E floccosum* The colony develops a central boss covered with pale buff velvet The rest of the colony is white velvet with no color on the reverse side There are several variations such as cottony powdery cerebriform white yellowish or reddish colonies

E rubrum develops in five days on glucose agar as a white knob with a red pigment developing and spreading slowly

E purpureum develops on the sixth to the eighth day as a white velvety colony On the tenth to the twelfth day it develops a reddish purple color at the base On the twentieth day the center of the colony is white with a powdery periphery Radial folds develop on glucose agar the purple color becomes accentuated but does not diffuse into the medium

EPIDEMIOLOGY AND GEOGRAPHICAL DISTRIBUTION

Epidermophytosis is an infectious and very frequently epidemic disease It is spread in gymnasia swimming pools locker rooms and is known to produce

EPIDERMOPHYTOSIS

Epidermophytosis which includes tinea cruris (eczema marginatum and in the tropics dhobie itch) and in some cases athlete s foot is a form of ring worm of the skin limited to the epidermis and to the nails seldom invading the corium and never affecting the hair or hair follicles The organisms are mem bers of the genus *Epidermophyton* Sabouraud 1910 and typified by the species *E inguinale* Sabouraud or *E floccosum* (Herz) Langeron and Milochevitch 1930

ETIOLOGY

On the basis that the organisms do not invade the hairs or hair follicles the fungi responsible for epidermophytosis have for the most part been considered as members of the genus *Epidermophyton*

In 1879 Lang proposed the name *Epidermidophyton* as a common name for what he believed to be fungous elements seen in the scales of psoriasis These elements were apparently artefacts Two years later Mégnin named the fungus causing a disease of the combs of fowl *Epidermophyton gallinae* which Sabouraud renamed *Achorion gallinae* It was not until 1907 that Sabouraud applied the name *Epidermophyton inguinale* to the organism of eczema marginatum It is in this way that the use of the generic name for a definitely different organism and disease has been allowed to stand in violation of the rules of nomenclature and has become effectively established in the literature The description of the organism as the species *floccosum* by Harz in 18,1 should however at least give the organism the name *Epidermophyton floc cosum* (Harz) Langeron and Milochevitch

In addition to *E floccosum* or *inguinale* there are several important and widely distributed organisms which may produce epidermophytosis Among them may be cited *E interdigitale* (Priestly) MacCarthy 19°5 an organism often described as a variety of *Ectotrichophyton* or *Trichophyton mentagro phytes E purpureum* (Bang) Dodge 193, or *Trichophyton purpureum* Bang 1910 a fungus which produces many of the lesions of epidermophytosis or eczema marginatum in the tropics (this latter organism produces an intense lesion which is extremely resistant to treatment) *E rubrum* Castellani 1910 also *T rubrum* Semon 1923 *E rubrum* is often confused with *E purpureum*

In young lesions the epidermophyta appear as fine branching filaments In older ones they show multiseptate filaments which form chains of arthrospores to rounded cells

In culture *E floccosum* develops as an elevated small colony greenish yellow in color velvety dry somewhat powdery and seldom over cm in diameter Pleomorphism takes place in from three to four weeks when the hyphae become white or gray The culture appears like a flattened cone with an irregular central apex and radial folds extending to the irregular border

Microscopically *E floccosum* shows many fuseaux 6 to 8 by o to 3o microns with four or five cells The fuseaux are thin walled sessile or the basal cell

region are similar in character As the lesions heal they may become dry crack and are painful The constant presence of perspiration in the inguinal region between the toes and in the axillae favors the growth of bacteria ac

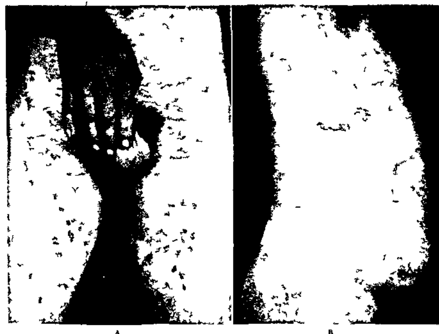


FIG 85 A Tinea cruris with satellite lesions caused by *Epidermophyton floccosum* B Tinea corporis caused by *Epidermophyton floccosum*

companied by constant friction this results in the formation of pustules with secondary maceration Scratching usually accentuates the condition Involvement of the toes and interdigital webs serves as a continual source of infection so that recurrences are common and eradication of all fungi unless the lesions are radically treated is almost an impossibility

Epidermophyton purpureum (*T purpureum*) has been frequently isolated from lesions of the toes and inguinal regions in the tropics This fungus produces lesions which are considered to be chronic and resistant to treatment On the toes and webs there is rarely seen any vesiculation or acute reaction the lesions are of the latent type There is little thickening or induration of the skin The edge of the lesion is sharply defined demarcating the infectious process from the normal skin On the hands or soles of the feet the infection may be diffuse or it may consist of isolated plaques dull red in color and slightly thickened Scaling is fine and branny and not complicated by large excoriations Itching is intense

Nail involvement may be unaccompanied by involvement of the fingers

epidemics among college students and athletes and in institutions army camps, and barracks Tinea cruris occurs particularly in epidemic form being spread by means of the athletic supporter Tinea of the feet also known as *athlete's foot* is likewise a common lesion and is usually spread through the use of the heavy woolen socks used in the gymnasium Among soldiers too the use of such socks is culpable (Fig 79)

In the Far East tinea cruris is usually known as dhobie itch and is attributed to contamination of the linen by the native laundryman who is known as a dhobie

The disease is common throughout the world and is especially prevalent in the tropics where the excessive perspiration of the inguinal region the axillae and the region between the toes offers an excellent substratum for the growth of the pathogenic fungi

PATHOLOGY

Tinea cruris is characterized by the production of sharply marginated inflamed lesions which often become eczematous The lesions show vesicles and secondary pustule formation due to bacterial contamination Fissuring scaling maceration and crusting are generally complications of epidermophytosis in later stages

Microscopically the picture is similar to that caused by Trichophytons in the same areas Particularly evident are edema marked hyperkeratosis definite parakeratosis acanthosis vesicle formation small round cell and leukocyte infiltration

SYMPTOMATOLOGY

Epidermophytosis involves the glabrous skin hands feet interdigital axillary and inguinal regions and nails When involving the hands feet glabrous skin and neck the lesions are similar to those caused by the species of *Trichophyton* The one exception is that the hairs are never invaded Lesions may also be present beneath pendulous breasts Lesions on the toes usually involve the webs producing interdigital tinea with subsequent thickening of the skin with resultant whitish or grayish white patches with subsequent cracking and fissuring accompanied by some itching

Tinea of the groin (Fig 80) or inguinal region usually commences as one or more small superficial circinate plaques which coalesce to form sharply marginated confluent symmetric inflammatory lesions somewhat brownish in color with elevated scaly borders They commonly appear on the inner aspects of both thighs in the form of a butterfly The lesions are infiltrated covered with minute vesicles and appear festooned The patches are adjacent to and contiguous with the scrotum or labia and the intergluteal regions When the disease becomes extensive it spreads along the sagittal line to involve such anterior and posterior regions as the perianal and umbilical regions intergluteal fold and mucosa of the vulva Fissuring is apt to occur about the anus causing severe and almost unbearable itching Lesions of the axillae and submammary

region are similar in character As the lesions heal they may become dry crack and are painful The constant presence of perspiration in the inguinal region between the toes and in the axillae favors the growth of bacteria ac

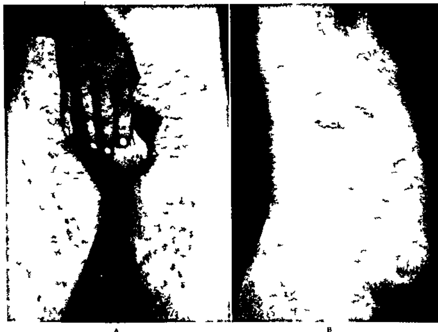


Fig 80 A Tinea cruris with satellite lesions caused by *Epidermophyton floccosum* B Tinea corporis caused by *Epidermophyton floccosum*

companied by constant friction this results in the formation of pustules with secondary maceration Scratching usually accentuates the condition Involvement of the toes and interdigital webs serves as a continual source of infection so that recurrences are common and eradication of all fungi unless the lesions are radically treated is almost an impossibility

Epidermophyton purpureum (*T purpureum*) has been frequently isolated from lesions of the toes and inguinal regions in the tropics This fungus produces lesions which are considered to be chronic and resistant to treatment On the toes and webs there is rarely seen any vesiculation or acute reaction the lesions are of the latent type There is little thickening or induration of the skin The edge of the lesion is sharply defined demarcating the infectious process from the normal skin On the hands or soles of the feet the infection may be diffuse or it may consist of isolated plaques dull red in color and slightly thickened Scaling is fine and branny and not complicated by large excoriations Itching is intense

Nail involvement may be unaccompanied by involvement of the fingers

(Fig 81) or toes The infection is deep accounting for its chronicity There is little inflammation in the subungual and paronychial tissues The infection is slow in its progress The nail shows longitudinal streaks yellowish or white

A





B

Fig 81 A Leukonychia trichophytica B Tinea of nails caused by *Epidermophyton (Trichophyton) purpureum*

in color These elongations crack the nail loosens and is infiltrated by cellular debris The nails become thin and may break off at the distal end leaving the thickened proximal portion

Tinea alba This is a form of generalized dhobie itch seen in the tropics where the arms legs chest or other parts of the body of the natives show a diffuse white powdery eruption as a result of infection with either *E rubrum* or *E purpureum* The margins of the lesions are raised and dotted with minute papules The disease is chronic After several years leukodermic areas develop at the sites of infection but fungi are not found

DIAGNOSIS

The appearance of epidermophytosis whether in the groin between the toes or on the hands or the feet cannot be diagnosed by inspection alone An accurate history is helpful in making the diagnosis The location of the disease in the groin its clinical appearance as described and the presence of satellite lesions are important diagnostically The diagnosis is made by culture and finding *E inguinale* However the disease may be confused with contact dermatitis erythrasma and so called seborrheic dermatitis Secondary infection adds considerably in confusing the original picture and should therefore be eliminated before any further work is done with the original infection

In epidermophytosis the lesion epidermophytide is often found Like the id produced by *Trichophyton* it is impossible to demonstrate fungi in such secondary lesions Trichophytin gives either a negative or a mildly positive reaction when the causative organism is *E floccosum* (*inguinale*) When *E purpureum* is the cause the reaction is negative in contrast to a positive response when *T gypseum* is the responsible agent

TREATMENT AND PROGNOSIS

Epidermophytosis is usually considered to be a recurrent disease However if the lesion is seen at an early stage it will usually respond to topical applications provided it is of the type due to *E floccosum* (*inguinale*) Lesions due to *E purpureum* are as a rule obstinate to all forms of treatment except in isolated cases and will recur if treatment is abandoned at too early a date The chief reasons for relapses are the cessation of treatment before the lesion is completely healed or reinfection from a focus of infection particularly in the webs of the toes

Treatment of epidermophytosis like the treatment of trichophytosis depends on the state of the lesion and its location Lesions on the hands arms or legs between the toes and the nails are treated in the same manner as are lesions of trichophytosis In intertriginous and hairy regions lotions and tinctures are preferable to salves pastes or ointments since the latter tend to produce irritation with a subsequent complication of bacterial infection A lotion found to be extremely beneficial in lesions of the axillae or groin is the following

℞	Bichloride of mercury	0 12 gm.
	Resorcinol	6 00 gm
	Alcohol (70%)	120 00 gm
Sig	Apply morning and night to affected parts	

Another excellent lotion is one prescribed by Wise and Sulzberger

℞ Menthol ¼ per cent phenol ½ per cent
(as antipruritics)
Resorcin 2–6 per cent
(as desquamative fungistatic and fungicidal agents)
Calamine lotion N F
(as vehicle antieczematous and drying agent)
Sig Apply morning and night to affected parts

On the soles and palms when the skin is extremely thickened or shows thick topped bullae a tincture made of 15 to 20 per cent salicylic acid in 90 per cent alcohol and painted on the affected parts once or twice daily is very effective as a desquamating agent Whitfield s ointment chrysarobin or thymol should be avoided for use in groin or axillae

Epidermophytides tend to disappear when the primary focus of infection regresses These lesions however may be intensely pruritic In these cases the use of a soothing antipruritic is advised An old but valuable shake lotion serves very nicely

℞	Phenol	1 gm
	Liquor carbonis detergens	3 gm
	Starch	20 gm
	Zinc oxide	20 gm
	Glycerin	30 gm
	Water	100 gm
Sig	Apply to affected areas	

ENDODERMOPHYTOSIS

Endodermophytosis is the name of a tropical skin infection characterized clinically by extensive scaly chalky patches which may appear in a circinate or concentric arrangement or in parallel lines the scales are large thin and firmly adherent The disease is caused by species of the genus *Endodermophyton* Castellani and Chalmers *E concentricum* (Blanchard) Castellani and Chalmers or *Trichophyton concentricum* Blanchard Among the many other names applied to this infection are

Tokelau (after Tokelau Island) Tokelau ringworm (Tilbury Fox) Bowditch ringworm (Bowditch being a name for Tokelau Island) Southwest gune (gune meaning skin) tinea imbricata (Manson) La Pita (from Peter the name of a native of Tamana one of the Gilbert Islands who according to Turner introduced the disease into Tokelau in 1850) herpes desquamans (Turner) Manson s herpes Turner s herpes gugo (a term used in the Marshal Islands) cascado (a term used in Malacca)

ETIOLOGY

Tinea imbricata or endodermophytosis is caused by members of the genus *Endodermophyton* (*Trichophyton*) Manson described an organism in the scales in 1872 and Tilbury Fox in 1874 likewise described filaments in material sent to him In 1896 Blanchard did not cultivate the fungus but named it *Trichophyton concentricum* as seen in scales

In 1910 Castellani cultured four strains which he regarded as *Endodermophyton concentricum* Later he cultured the fungus from three cases in Ceylon In the scales *T concentricum* is simply an interlacing network of closely compact filaments which break up easily into arthrospores or rectangular cells

In culture on glucose agar the colony develops as a central cerebriform or crinkled colony dirty white becoming light amber or light brown in color with the radially furrowed periphery covered with a short white growth The reverse is deep amber in color Microscopically the center of the colony shows thick walled arthrospores which give rise to chlamydospores or large hyaline swollen bodies No other types of spores are seen There is irregular branching of certain short lateral outgrowths

EPIDEMIOLOGY AND GEOGRAPHICAL DISTRIBUTION

Endodermophytosis although considered to be endemic in certain areas as that described by da Fonseca along the Rio San Miguel in Matto Grosso Brazil or in the Island of Tokelau is not generally considered to be a spreading disease responsible for epidemics The probable focus of the disease is attributed to the Malay Peninsula whence it spread southward and eastward as well as westward through the migration of the natives The disease is extremely common at the present time in the Malay Peninsula parts of Indo-China Southern China Borneo Samoa Java the Solomon Islands Fiji Sumatra New Guinea Burma Ceylon Gilbert Islands many other Pacific islands and the Philippines It is also present in South America Africa India and many other countries

It is particularly prevalent in warm moist climates where the temperature ranges from 80 to 90 F Manson makes the statement that the disease prevails where coconuts thrive

PATHOLOGY

The organism does not attack the hair but invades the epidermis and extends deeply into the corium much deeper than in the commoner *Trichophyton* infections As a result the microscopic picture is similar but perhaps more intense than that seen in trichophytosis This is characterized by edema which may be accentuated as a result of scratching due to the intense itching marked hyperkeratosis as well as parakeratosis acanthosis some vesicle formation small round cell and leukocytic infiltration In many cases the blood shows a marked eosinophilia This has been attributed in some cases to intestinal worms

However the worms are not found in many cases In cases which are chronic the eosinophilia is marked and anemia may be present

SYMPTOMATOLOGY

The disease begins as one or more small round or oval somewhat raised or papular dark reddish patches which are extremely pruritic The central area of the patch cracks as it extends peripherally and scales form at the periphery due to the lifting up of the epidermal lamellae The free end of the upturned scale is directed toward the center of the lesion and the attached portion becomes more deeply pigmented While this process is going on new horny material is formed in the center This again goes through the same process of cracking with peripheral extension and scale formation This succession of events is repeated until there is formed a large patch of either concentric rings or a mottled or imbricated lesion which Manson has compared with the formation of rings or ripples caused by throwing a pebble in a pool of water Very often when there are several primary lesions usually multiple infections or successive primary lesions due to autoinoculation the rings coalesce to form polycyclic or concentric designs This may then be compared to the dropping of several pebbles in a pool of water The number of concentric rings varies Castellani noted eight or ten The scales vary in size but are large up to one half inch in length dirty grayish or brownish in color and of the consistency of tissue paper The largest scales are seen on the back when the scales are removed there is visible a group of dark lines When the eruption becomes generalized the configuration may be lost and the lesion simulates a mild ichthyosis In chronic cases the scales become thick and horny so that the lesions appear as though coated with clay The lesions may be present on all parts of the body although the face axillae palms and soles are rarely affected The nails may be infected becoming thick rough and cracked The general health is seldom affected and aside from the intense itching symptoms are lacking

DIAGNOSIS

The diagnosis of tinea imbricata is relatively simple The concentric or imbricated formations are characteristic The development of the scales and their tissue paper consistency and size are unlike other scaling processes However it is best at all times to look for the fungus in scrapings The disease should be differentiated from other tineas which usually show inflammation with smaller scales Ichthyosis should be ruled out in the more generalized lesions Ichthyosis is usually congenital is present from childhood on does not ooze is not infectious is usually limited to the extremities and differs somewhat in its clinical expressions

PROGNOSIS AND TREATMENT

Endodermophytosis has not a tendency to regress spontaneously It is chronic and although some areas may be cleared by treatment recurrences are the rule The general health is not usually affected but the intense itching is a constant

source of annoyance and often as a result of scratching leads to secondary infection and disfigurement Anemia may be found in the old chronic cases and this may lead to weakness emaciation and inability of the patient to work

A number of methods have been suggested for the treatment of this disease Castellani advised the use of resorcin dissolved in tincture of benzoin (resorcin ʒii tincture benzoin compound ℥i) or the application of chrysarobin ointment (5 per cent) These are applied once or twice daily and hot baths with the use of sand soap are prescribed twice weekly Caution should be used in applying these ointments and the reaction should be kept under close observation when resorcin is used on the body Dermatitis may result from the use of this drug The use of chrysarobin on the body should likewise be carefully checked since acute dermatitis may follow its use Chrysarobin is a toxic drug The usual ointments containing sulfur ammoniated mercury and other parasiticidal agents have proved of little value Castellani s fuchsin paint has proved of value

℞	Saturated alcoholic solution of basic fuchsin	10 0 gm
	5 per cent aqueous solution of phenol	100 0 gm
	Filter and add	
	Boric acid	1 0 gm
	Wait two hours and add	
	Acetone	5 0 gm
	Wait two hours and add	
	Resorcinol	10 0 gm
Sig	Apply to affected parts	

Deek s ointment has also been used successfully

℞	Salicylic acid	4 0 gm
	Mercurial ointment	4 0 gm
	Bismuth subnitrate	12 0 gm
	Anhydrous wool fat	100 0 gm

Deek s preparation is quite strong and occasionally causes dermatitis but the strikingly good results obtained are sufficient for the patient to submit willingly to this treatment

FAVUS

Favus (tinea favosa tinea capitis favica dermatomycosis favosa honeycomb ringworm) is a fungous infection of the skin caused by members of the genus *Achorion* and characterized by the formation of sulfur yellow crusts in the form of cups or scutulae about the affected hair of the scalp with patches of dermatitis on the glabrous skin It has a typical mouse odor The nails may also be affected

ETIOLOGY

Favus is caused by members of the genus *Achorion* The most common species is *A schonleinii* (Lebert) Remak 1845 which is referred to as the human type

since it is the usual organism found in human lesions Several species have been found in animals some of which may be inoculable into man Of the latter the common ones are *A muris* (Cluge and d Ukedem) Dodge 1935 also known as

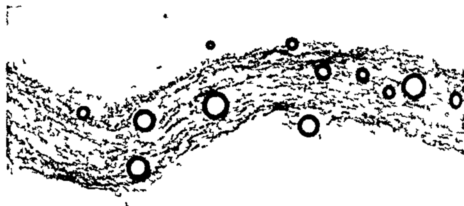


Fig 82 Hair infected with *Achorion schonleinii* Note gas bubbles

A quinckeanum Bodin 190 which causes mouse favus *A gallinae* (Mégnin) Sabouraud 1910 causing favus about the head of the turkey and domestic fowl found also on man *A gypseum* Bodin 1907 perhaps similar to *Microsporum fulvum* which is responsible for favus with the production of scutula on the cat dog and horse rarely on rats mice or men *A passerinum* Fischer 19 8 favus of the canary inoculable into man with the production of herpetic lesions *A serisei* Cazalbou 1913 causing favus of the horse in Madagascar *A caninum* (Costantin and Sabrazès) Dodge 1935 favus of the dog inoculable to man mouse and dog There are also several other species found in man such as *A violaceum* Bloch 1911 in which the lesions resembled those caused by *Trichophyton* *A cupressiforme* Aoki 1917 producing favus turriformis and favus confertus on the glabrous skin with lesions also on the scalp

In the lesions *Achorion* is made up of chains of short rectangular cells (arthrospores) occurring on the hair shaft The fungus may invade the hair and there can be found spaces in the hair substance An outstanding characteristic of the infected hair is the presence of gas bubbles which are apparently formed as a result of the decomposition of the fungous elements and which are responsible for the typical mouse odor In the scutulum or cup the organism consists of short branched filaments and spores while in the superficial cutaneous lesions (glabrous skin) there are a number of hyphae (Fig 8)

In culture *Achorion schonleinii* develops slowly requiring several weeks before there is identifiable growth It appears at first as a small elevated irregular plaque wax colored The surface becomes markedly irregular or cerebriform The mycelium penetrates into the substratum splitting it Pleomorphism is not uncommon the culture developing a white downy appearance similar to *A muris* *A muris* or *A quinckeanum* on the other hand grows

rapidly beginning as a small white downy disc which enlarges and forms a few concentric furrows and irregular folds around the margin *A gypseum* resembles *Microsporum fulvum* so closely that it is not unlikely that they are identical species *A violaceum* is similar to *Trichophyton violaceum* culturally

Microscopically *A schonleinii* shows in culture chlamydospores and aleurospores occasionally macrospores The hyphal tips are often swollen and branch in the form of candelabra (favic candelabra) which are diagnostic

EPIDEMIOLOGY AND GEOGRAPHICAL DISTRIBUTION

Although favus is quite common in certain countries particularly in Europe and Asia and has been reported in South America Africa Formosa Madagascar the United States and other countries of the world both in the temperate and tropical zones it is not essentially a disease of any special area It can be said to be universal

Favus is not especially an epidemic disease It has been reported as occurring in families The disease is moderately infectious and is spread by actual contact

PATHOLOGY

A schonleinii invades the skin and the hair follicles producing marked inflammation both in the lining of the follicle and in the surrounding skin The crusts formed in the tissue are made up of a central zone of polyhedral cells varying in size These cells grow upward in the follicle and surround the hair This zone is then surrounded by chains or filaments of cells which are intertwined The periphery of the crust is made up of variously sized and shaped cells The crust develops around the hair in a convex manner to form the early stage of the cup As the cup develops it becomes concave with a raised periphery in the form of a collar This forms a cuplike structure which is termed the scutulum The scutulum grows into the epidermal tissue and replaces the normal tissue with a resultant atrophy scar formation and alopecia Sulfur yellow in color the scutulum becomes firmly attached and when forcibly removed reveals bleeding points The epidermis exhibits edema parakeratosis little perivascular infiltrate lymphocytes and leukocytes There is also a mild acanthosis

SYMPTOMATOLOGY

Favus affects the scalp chiefly but also the beard smooth skin and nails It manifests itself by the formation of crusts or scaling lesions with the formation of typical yellow or sulfur colored crusts in the form of cups termed scutula These formations also called godet by the French may vary from the size of a pin head to that of a pea The lesions begin as small scaly patches as a result of a follicular or subepidermal invasion and are seen as miliary punctate formations with or without vesicles Within a few weeks the crusts take on a cup- or saucer like shape through which a hair protrudes As the scutula become older the edges become elevated fringelike and firmly attached to the underlying skin When the crusts are forcibly removed a depressed bleeding surface



Fig 83 Favus of scalp

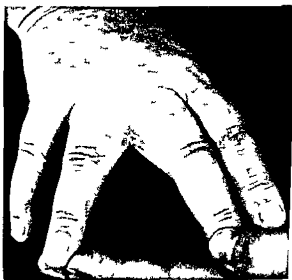


Fig 84 Erosio interdigitale blastomycetica

is exposed The underlying skin is destroyed with resultant scar formation The hairs become dry brittle lusterless fall out and permanent alopecia may result The crusts may extend peripherally or they may be heaped up to form thick masses the older portion of which becomes pearly in color while the younger section is sulfur-colored The lesions may coalesce to form large plaques The scutula are particularly characterized by a peculiar mouse odor Kerion may be formed on the scalp by *A schonleinii*

On the glabrous skin the lesions may manifest themselves in the form of scutula but generally they appear as acute dull red discoid patches with vesiculation In the center cuplike scutula are found in varying degrees of development Lesions of the glabrous skin are followed by less scarring than that seen on the scalp (Fig 83)

Favus of the nails differs little from onychomycosis due to other organisms and is differentiated either by finding typical scutula elsewhere on the body or by isolating the organism

Like other dermatomycoses favus may produce allergic manifestations known as favides These lesions are analogous to other ides

DIAGNOSIS

Finding of scutula or sulfur colored cuplike structures on the scalp beard or glabrous skin together with the typical mouse odor are usually sufficient for diagnostic purposes These are especially evident in the early stages of the disease However when the lesions are chronic and secondarily affected they may simulate eczema seborrheic dermatitis psoriasis and other lesions In these cases the location of the lesion the mouse odor and the finding of the fungus especially the characteristic formation in the hair with the formation of gas bubbles should easily differentiate favus from other complications

PROGNOSIS AND TREATMENT

Favus is usually a chronic disease and may persist for a number of years It may clear up spontaneously with resultant cicatrices and permanent alopecia where hairy parts are involved On the scalp however favus is extremely resistant to treatment unless the proper therapeutic measures are taken

In the hairy regions such as the scalp the method of choice is to remove as much of the crust formation as possible by means of wet packs and then to epilate all infected hairs This can be done with the proper use of roentgen rays or by manual epilation The infected hairs can be detected with the Wood light They appear as greenish luminous stubs somewhat less luminous than *Microsporum* infected hairs In mild cases several of the treatments useful in combating other fungous infections of the scalp may be used successfully

Treatment of lesions of the glabrous skin can be carried out with good results by using ointments containing 5 to 10 per cent ammoniated mercury 10 to 20 per cent sulfur or 5 to 10 per cent chrysarobin Tincture of iodine may be used effectively Fungous vaccines apparently have no value

CHAPTER LVII

MYCOSES WITH SYSTEMIC INVOLVEMENT

MORRIS MOORE

MONILIASIS

UNDER THE GENERAL HEADING OF MONILIASIS OIDIOMYcosis or soorpilz there fall terms applying to specific conditions such as onychomycosis (nails) paronychomycosis (paronychial involvement) erosio interdigitale blastomycetica (webs of fingers) intertrigo (intertriginous areas) perlèche (angles of mouth) and others It is a group term covering a number of yeastlike infections of the skin nails mucous membranes and viscera The chief organisms are members of the genus *Monilia* (*Candida Syringospora*)

ETIOLOGY

The micro organisms responsible for the clinical syndrome moniliasis are classified as members of the genus *Monilia* as it is known generally or *Candida Syringospora* or *Mycotorula* as it is known to the mycologist The classification of the yeastlike organisms of this group have been critically investigated and discussed by numerous workers On the basis of priority Dodge retains the name *Syringospora* Quinquaud 1868 Ciferri and Redaelli adhere to the genus *Mycotorula* Will On the other hand Diddens and Lodder favor *Candida* as emphasized by Berkhout The generally used term is *Monilia albicans* Zopf 1890 In any event it would appear that all these names are synonymous

The species of *Monilia* are many On the basis of sugar reactions Castellani has described a large number in his Manual of Tropical Medicine This he revised in 1937 Martin Jones Yao and Lee have also prepared a method for the classification of *Monilia* which Martin and Jones further studied in 1940

In sections of tissue secretions excretions or exudates of the affected parts *M albicans* is seen as a simple or budding yeastlike cell ovoid to spherical 3 to 10 microns in diameter or in distorted or sclerotic variations occurring in large clumps

In culture the organism is seen as a creamy thick convex colony The cells reproduce by polar budding followed by the formation of elongated forms with septate hyphae to produce an intertwining mycelium called a pseudomycelium

Ovoid or spherical blastospores in simple verticils form at the septa Terminal cells or chlamydospores occur on cornmeal agar usually in cluster form or rarely as short chains The fungus liquefies gelatin and ferments sugars

EPIDEMIOLOGY AND GEOGRAPHICAL DISTRIBUTION

Moniliasis is not regarded as an epidemic disease The organisms are saprophytic in nature and the disease generally occurs spontaneously It is highly contagious and may spread from person to person as a result of contact Moniliasis is world wide in its distribution Moisture and warmth contribute greatly to the ability of the fungus to grow

PATHOLOGY

Moniliasis manifests itself either as a localized or generalized disease of the skin or the mucous membranes in the form of plaques and then spreads to become systemic On the skin the lesions produce vesicles pustules crusting and scaling with deeply inflamed red thickened moist lesions Systemically in the lungs gastro-intestinal tract and other affected organs there is conspicuous edema

Microscopically the epidermis shows marked hyperkeratosis with vesicle formation There is inflammation of the cutis with an infiltrate of epithelioid cells leukocytes giant cells and fibroblasts in tuberculoid formation In the lungs there are numerous tubercles of the type seen in granulomatous infections with many leukocytes epithelioid cells and giant cells surrounded by fibroblasts with or without central necrosis The affected pulmonary tissues usually show hyperemia with edema The alveolar tubules show narrowing as a result of the edema

SYMPTOMATOLOGY

Moniliasis manifests itself as a *localized* or *generalized* disease In the case of cutaneous localized lesions moniliasis is limited to definite areas or regions of the body or it may involve several areas in the same manner that characterizes other fungous infections The lesions may be acute or chronic either inflammatory or subdued

Shelmire in 1925 and Lewis and Hopper in 1938 listed the various lesions caused by *M albicans* These included the following

Localized Moniliasis

(1) *Onychomycosis and paronychial involvement* In these lesions one or more nails of either of the fingers or toes are involved but the disease spreads easily to the other nails The paronychial tissue is generally involved at first becoming swollen and painful to the touch When incised a thin purulent discharge is exuded from the nail bed The nails become hard greatly thickened distorted and eroded particularly at the proximal edges and show transverse ridging Tinea unguium differs in that there is usually no paronychial involvement and the nails become lusterless fragile and yellowish in color

(2) *Intertrigo* This term is applied to lesions of the axillae inguinal region interdigital spaces inframammary folds intergluteal fold and the umbilicus The lesions are bright red somewhat macerated exuding patches with an irregular or scalloped border As a result of friction of the opposing surfaces the lesions tend to become raw Surrounding the main patch may be seen small vesicular or pustular lesions termed the satellite lesions The patches may extend to involve large areas particularly if the individual is obese and perspires freely As variants of the intertriginous type of lesion there are perleche and erosio interdigitale blastomycetica (Fig 84)

(3) *Perleche* This lesion affects the labial commissures bilaterally A thickened and somewhat macerated lesion develops showing fissures which produce much soreness and discomfort The disease usually extends to the mucosa Perlèche is infectious easily transferable and is found often in epidemic form in orphanages It may frequently be found in women living on a pellagra producing diet or in patients lacking riboflavin which deficiency may be a contributing factor

(4) *Erosio interdigitale blastomycetica* This form of intertrigo affects the webs of the fingers and is usually associated with moniliasis of the nails and paronychial tissue The third or fourth interdigital web is the almost invariable site of infection The lesions are tender with a bright red base moist surface are superficially inflammatory and have a raised somewhat macerated border in which the organisms can be found The infection is especially prevalent in laundresses and dish washers

(5) *Water bath dermatitis* Continuous immersion of the hands or feet or other parts of the body in baths or application of wet packs or dressings over a long period of time may give rise to lesions of moniliasis as a result of secondary infection The skin becomes macerated and peels off revealing a red base Satellite lesions made up of vesicopustules may be noted

(6) *Thrush* This involves the oral cavity It is found usually among children and is attributed to *M albicans* It manifests itself as an inflammation of the oral mucosa with the production of whitish loosely adherent plaques sometimes resembling curdled milk When the plaques are forcibly removed bleeding surfaces may be revealed The disease may be epidemic among babies or infants in institutions

(7) *Glossitis or beefy tongue* a manifestation often associated with stomatitis and *M albicans* presents itself as hyperemia of the fungiform papillae Aphthous ulcers may be present The tongue is sensitive to hot liquids spices and tobacco smoke In chronic cases the tongue becomes smooth is beefy red in color enlarged and occasionally mottled Some cases of black tongue or lingua nigra may be due to yeastlike organisms

(8) *Pruritus ani or pruritus vulvae* may be caused by *M albicans* The lesion develops severe itching when the anal orifice or labia are involved As a result of scratching there is maceration inflammation and occasionally secondary infection Chemical irritation may complicate the lesion as the result of treatment or otherwise

(9) *Vulvovaginitis M albicans* may often cause lesions which extend into

the vulva There is usually pruritus associated with an inflammatory reaction and a thin discharge Diabetes accentuates the lesion due to the ability of the fungus to utilize the dextrose advantageously The disease occurs in infants and



Fig 85 A Cutaneous moniliasis B Moniliasis of plantar surfaces

children as well as in adults Infantile eczema may be caused by *M albicans* as a result of delivery through an infected vagina Perleche in infants may likewise be due to the same source Vaginitis manifests itself in many forms being creamy (containing pus and mucus) resembling oral thrush vulvitis producing considerable discharge with or without inflammation and accompanying intertrigo ulcerative vulvitis showing superficial ulceration with pain lymphangitis and adenitis accompanied by tenderness pseudoleukoplakic vulvitis with whitish or opaque plaques which are difficult to remove eczematoid vulvitis with vesicopustules spreading to the folds and other varieties all attributable to *M albicans*

Penile lesions may be characterized by pin head sized or larger scaly red patches usually present on the glans or about the prepuce Penile lesions may simulate vaginal lesions Genitocrural lesions in the male are not uncommon

Generalized Moniliasis

Generalized moniliasis which is rare is a chronic resistant disease manifesting itself in widespread cutaneous (Fig 85) involvement usually comprised of circumscribed lesions Generalized involvement may present all of the hitherto mentioned lesions in one individual Pustules may be found in some parts of

(2) *Intertrigo* This term is applied to lesions of the axillae inguinal region interdigital spaces inframammary folds intergluteal fold and the umbilicus The lesions are bright red somewhat macerated exuding patches with an irregular or scalloped border As a result of friction of the opposing surfaces the lesions tend to become raw Surrounding the main patch may be seen small vesicular or pustular lesions termed the satellite lesions The patches may extend to involve large areas particularly if the individual is obese and perspires freely As variants of the intertriginous type of lesion there are perleche and erosio interdigitale blastomycetica (Fig 84)

(3) *Perleche* This lesion affects the labial commissures bilaterally A thickened and somewhat macerated lesion develops showing fissures which produce much soreness and discomfort The disease usually extends to the mucosa Perleche is infectious easily transferable and is found often in epidemic form in orphanages It may frequently be found in women living on a pellagra producing diet or in patients lacking riboflavin which deficiency may be a contributing factor

(4) *Erosio interdigitale blastomycetica* This form of intertrigo affects the webs of the fingers and is usually associated with moniliasis of the nails and paronychial tissue The third or fourth interdigital web is the almost invariable site of infection The lesions are tender with a bright red base moist surface are superficially inflammatory and have a raised somewhat macerated border in which the organisms can be found The infection is especially prevalent in laundresses and dish washers

(5) *Water bath dermatitis* Continuous immersion of the hands or feet or other parts of the body in baths or application of wet packs or dressings over a long period of time may give rise to lesions of moniliasis as a result of secondary infection The skin becomes macerated and peels off revealing a red base Satellite lesions made up of vesicopustules may be noted

(6) *Thrush* This involves the oral cavity It is found usually among children and is attributed to *M albicans* It manifests itself as an inflammation of the oral mucosa with the production of whitish loosely adherent plaques sometimes resembling curdled milk When the plaques are forcibly removed bleeding surfaces may be revealed The disease may be epidemic among babies or infants in institutions

(7) *Glossitis or beefy tongue* a manifestation often associated with stomatitis and *M albicans* presents itself as hyperemia of the fungiform papillae Aphthous ulcers may be present The tongue is sensitive to hot liquids spices and tobacco smoke In chronic cases the tongue becomes smooth is beefy red in color enlarged and occasionally mottled Some cases of black tongue or lingua nigra may be due to yeastlike organisms

(8) *Pruritus ani or pruritus vulvae* may be caused by *M albicans* The lesion develops severe itching when the anal orifice or labia are involved As a result of scratching there is maceration inflammation and occasionally secondary infection Chemical irritation may complicate the lesion as the result of treatment or otherwise

(9) *Vulvovaginitis* *M albicans* may often cause lesions which extend into

treatment but responds eventually to iodide therapy and deep roentgen ray therapy The severe type is very often fatal

As prophylactic measures cleanliness and dryness are important as well as loose clothing and the use of bland dusting powders Moniliasis is often associated with diabetes Control of the diabetes aids considerably in combating the fungous infection

Treatment in moniliasis as in other dermatomycoses should be aimed at eradicating the fungi The affected cutaneous lesions should be kept dry Simple cutaneous lesions may be adequately checked with 10 per cent silver nitrate or per cent alcoholic gentian violet Crystal violet is more fungistatic *and may be substituted often with better results Chronic onychomycosis or* paronychial involvement often succumbs to roentgen rays In paronychia 5 per cent chrysarobin in chloroform can be used to advantage Erosio interdigitale blastomycetica is often completely controlled by the frequent application of undiluted balsam of Peru The use of a 10 per cent sulfathiazole ointment is sometimes of very great benefit Mouth lesions are amenable to astringent mouth washes The use of per cent aqueous gentian violet has given excellent results

Moniliids of the hands arms or body may be treated in the same manner *as are ids of other fungi Antipruritics soothing and drying shake lotions* are advisable

Vaginitis or vulvitis can be cured as a rule by swabbing the affected parts with 2 per cent aqueous gentian violet Frequent vaginal douches are advisable in order to keep the organisms from multiplying Potassium permanganate 1 5000 will serve for this purpose

The results obtained from the use of an extract of *M albicans* (oidiomycin) have not been too encouraging At best vaccines of this type may be of value diagnostically

Pulmonary moniliasis of the mild type usually disappears with the use of iodide therapy—potassium iodide saturated solution 15 drops three times daily The dose should be increased to tolerance and the treatment continued for several weeks after symptoms subside In the severe type the additional use of deep roentgen ray therapy is advised Sulfanilamide or sulfathiazole may be of value

SPOROTRICHOSIS

Sporotrichosis is a granulomatous disease process usually confined to the cutaneous or *subcutaneous structures It spreads through the lymph channels* to produce typical and characteristic lesions or it may involve the internal viscera and bony structures to present a confusing picture The infection is subacute or chronic and is caused by members of the genus *Sporotrichum*

ETIOLOGY

Several different species of *Sporotrichum* can cause sporotrichosis The most common are *S schencki and S beurmanni (S schencki beurmanni S schencki beurmanni var beurmanni)* In tissue or pus the organism appears as a short

the eruption These become dry forming scales on the surface Maceration and then desquamation usually follow scratching exposing a bright red moist surface with a raised thickened periphery

Moniliasis of considerable duration has a peculiar yeasty odor

As with other dermatomycoses *Monilia* produces an id reaction termed *monilid* or *levuride* These lesions are either localized or widespread and consist of erythematous closely packed intra epidermal vesicles which may be exudative They are generally found on the hands legs or flexures although generalized monilids are not uncommon Fungi are seldom found in these lesions which develop as a result of the spread of either the fungus or its toxin through the bloodstream from foci in the glabrous skin nails mouth vagina gastro-intestinal tract or systemic involvement

Gastro intestinal involvement is usually asymptomatic but the organism can be cultured either from the sputum or from the stools

Systemic Moniliasis

Systemic moniliasis usually refers to bronchial or pulmonary involvement The lesions spread from the oral cavity into the bronchi and lungs where they are clinically of three types—*mild intermediary* or *severe* The mild type is accompanied by a slight cough with yellowish or greenish mucopurulent but not bloody expectoration there is no fever It may subside or develop into the intermediary type simulating an early tuberculosis with severe coughing dyspnea an irregular or continuous fever with or without hemoptysis The evidence of bronchitis may be the beginning of the severe type In this stage which may often be fatal the lungs are unilaterally or bilaterally involved with the pleura usually affected The picture is that of pulmonary tuberculosis with irregular fever night sweats loss of weight frequent coughs and expectoration of a tuberculous nature

DIAGNOSIS

The diagnosis of moniliasis rests on the finding of the yeastlike cells either in the cutaneous scrapings or in the sputum They must be found on repeated occasions to rule out secondary invaders and bacteria since the fungus may invade tissue which has a lowered resistance As they may overgrow primary bacteria it is well to establish their pathogenic nature *M albicans* however is not usually a chance skin contaminant

Moniliasis of the skin should further be differentiated from bacterial infections particularly in intertriginous areas Lesions of the hands feet or nails should be distinguished from the dermatomycoses Pulmonary involvement often resembles tuberculosis

PROGNOSIS AND TREATMENT

Cutaneous moniliasis of the localized type is amenable to treatment Generalized cutaneous involvement is usually chronic resistant to treatment and relapses may occur Systemic involvement if of the early or mild type may clear spontaneously The intermediary type is usually chronic and resistant to

vessels having a syphiloid appearance Occasionally there may be seen some what enlarged macrophages or mononuclear leukocytes within which there may be seen rarely the cigar or oval shaped somewhat encapsulated form of the fungus

SYMPTOMATOLOGY

Sporotrichosis usually begins as a small abscess at a site of trauma This enlarges to form a nodule which becomes fluctuant in the center and then ruptures spontaneously The purulent material escapes onto the surface of the adjacent skin resulting in secondary lesions The original lesion may heal spontaneously or it may ulcerate This serves as a primary lesion from which the organism spreads through the lymph channel to produce a chain of subcutaneous nodules The disease may spread to involve other parts of the body or become systemic De Beurmann and Gougerot for the purposes of clinical classification have divided the disease into the *cutaneous subcutaneous extracutaneous* and *visceral forms*

Gummatous disseminated sporotrichosis includes (1) non ulcerating gummatous forms (2) ulcerating disseminated subcutaneous sporotrichosis including the tuberculoid syphiloid ulcerating polymorphic and furuncle like types (3) large multiple disseminated abscesses (4) mixed forms including polymorphic gummas large abscesses secondary lymphangitis dermic and epidermic lesions and associated involvement of the mucous membranes and internal viscera and organs

Localized sporotrichosis subcutaneous or *cutaneous* includes (1) gummatous lymphangitis with or without an initial sporotrichotic chancre and sporotrichotic adenitis (2) inoculation chancre and adenitis without lymphangitic involvement and without gummatous formation (3) primary sporotrichotic chancre without lymphangitic involvement (4) gummatous lymphangitis without the chancre (5) gummatous sporotrichosis in steps localized to one area without lymphangitic involvement

Extracutaneous forms or *systemic sporotrichosis* including involvement of the mucous membranes muscles osseous structures joints synovial membranes and other internal viscera or organs These may be and usually are associated with primary or secondary cutaneous involvement

DIAGNOSIS

The diagnosis of sporotrichosis is often simple in the lymphangitic type (Fig 86) of the disease since the clinical features are pathognomonic However the chain of nodules following along the lymph channel and originating from a primary focus of infection on a finger the wrist or the hand following a trauma should be carefully differentiated from tularemia Squamous cell carcinoma may spread by way of the lymph channel and present a similar picture In localized or generalized lesions syphilis and tuberculosis should be ruled out This may be done by culturing the responsible fungus Smears are of little value since it is extremely difficult to demonstrate the fungus in slide

rodlike blunt cell 1 to 3 by 2 to 5 microns occurring singly or in groups or as an ovoid cell either freely in the necrotic material or in the mononuclear leukocytes or macrophages It is gram positive with a capsule like colorless periphery

When first cultivated on solid medium the organism develops a pin point colony within two or three days It is white at first becoming light to dark cinnamon in color when the fructifications develop The colonies then become more or less confluent and take on a cerebriform or vermiculate appearance

Microscopically the fungus is seen as a growth of tangled interlacing filamentous mycelium the hyphae being approximately 1 to 5 microns in diameter depending on the type of medium used Conidia are many spherical ovoid or pyriform pedicellate or sessile and grow singly or in groups measuring approximately 2 to 4 by 2 to 6 microns and are found laterally or terminally Oidioid cells may form singly budding or may develop into chains of spherical ovoid or arthrosporous like cells

EPIDEMIOLOGY AND GEOGRAPHICAL DISTRIBUTION

Sporotrichosis is not an epidemic disease It occurs spontaneously and sporadically since the organism is saprophytic in nature The condition is found chiefly in rural districts among farmers and those in contact with soil and with animals such as horses or cows Gastineau Spolyar and Haynes reported six cases occurring among florists Sporotrichosis is widespread throughout the world The greater number of cases have been reported from France with reports from the United States and numerous countries in Europe and South America In the United States the disease is considered endemic in the Mississippi Valley particularly in the Mississippi Basin

PATHOLOGY

Sporotrichosis is a granulomatous disease and as such may simulate tuberculosis syphilis neoplasms and other mycotic granulomata In the cutaneous form nodules ulcers gummas and abscesses are seen The systemic forms involve the mucous membranes muscles glands bones and joints articular and synovial membranes gastro intestinal tract cerebrospinal system and pulmonary system

Microscopically the tissue reaction resembles very closely that of other mycotic granulomata and may be confused with tuberculosis or syphilis In the epidermic layers there is an intercellular and intracellular edema and an irregular acanthosis either marked or moderate and at times suppurating foci which are more particularly evident in the ulcerating type of lesion The granulomatous nature of the lesion is fairly well distinguished by a nodular histopathology The center of the lesion usually shows abscesses of varying size within which are seen necrotic masses leukocytes and richly stained cells and giant cells of the Langhans type The whole is thus more or less tuberculoid in appearance Surrounding the lesion is a rich cellular infiltrate made up of young connective tissue cells plasma lymphocyte and mast cells and dilated blood

manifestations It represents a group of closely allied multiform clinical conditions No organ or tissue is immune thus the disorder not only involves the cutis but also the viscera and bony structures in its systemic spread The disease processes vary somewhat in the various continents with different causative agents In North America it is termed Gilchrist s disease or North American blastomycosis in South America it is called paracoccidioidal granuloma or Lutz Splendore-de Almeida disease and in Europe Busse Buschke s disease or European blastomycosis is alluded to when blastomycosis is used

NORTH AMERICAN BLASTOMYCOSIS

ETIOLOGY

The causative organisms of Gilchrist s disease are members of the genus *Zymonema* Beurmann and Gougerot 1909 (*Z dermatitidis Z capsulatum*) These are often referred to as *Blastomyces* (*B dermatitidis*) Costantin and Rolland 1888 or *Gilchristia* Redaelli and Ciferri 1934 The fungi occur in tissue as single or budding yeastlike cells thick walled double contoured and they measure approximately 5 to 12 microns in diameter usually about 7 microns In old necrotic lesions one may occasionally see simple branching cells which may attain a length of o microns

When cultured the colonies of the fungus are generally yeastlike at first then they become prickly or coremioid in appearance and finally profuse and cottony with aerial mycelium At first white the color changes to chamois and then light brown The colonies develop radiating ridges and concentric rings of growth There are two species *Zymonema dermatitidis* (Fig 87) which goes through the above color changes and *Z capsulatum* which remains white

Microscopically the cultures show septate branching hyphae which measure 2 to 4 microns in diameter associated with many pyriform or round conidia pedicellate or sessile measuring 5 microns in diameter racquet mycelium 5 to 6 by 3 to 5 microns chlamydospores terminal or lateral 5 5 to 7 5 by 1 to 15 microns or spherical 7 microns in diameter and ascogenous spherical cells 8 to 15 microns

EPIDEMIOLOGY AND GEOGRAPHICAL DISTRIBUTION

Gilchrist s disease is not epidemic Infection usually develops at the site of a trauma The disease is particularly prevalent among farmers although people in the city have also been infected The organism may be spread through horses and cattle Blastomycosis is supposedly endemic in certain areas of the United States particularly the Mississippi Valley and outlying districts However it has been reported from many other localities

PATHOLOGY

Both grossly and histopathologically the lesions of blastomycosis resemble closely those of tuberculosis a neoplasm or syphilis There are certain characteristics however which tend to differentiate these diseases The pathologic changes of blastomycosis in the skin occur as pustules ulcerations nodules

preparations In tissue Unna's polychrome methylene blue may be used to demonstrate the fungus Complement fixation tests may be used diagnostically as well as sporotrichin (analogous to trichophytin) but these are not always reliable



Fig 86 Lymphangitic sporotrichosis

PROGNOSIS AND TREATMENT

Surgical treatment is not advocated Roentgen ray therapy locally may be used but results are not encouraging Potassium iodide given orally 15 drops three times daily of saturated solution and increased 5 drops daily and then to tolerance is usually a specific If iodide by mouth is not tolerated sodium iodide may be given intravenously Locally Burrow's solution (1 15) may be applied as a dressing for thirty minutes several times daily The iodides should be continued for several weeks following the disappearance of lesions

BLASTOMYCOSIS

The term blastomycosis in its medical sense represents a more or less definite clinical syndrome with a multiplicity of causative yeastlike species In its wider application and as used by medical men in general it includes all those diseases which are produced by budding yeastlike organisms All of the expressions of the disease are granulomatous in nature and protean in their

gummas and papillomas granulomatous in nature In the internal organs the disease manifests itself as miliary or large sized nodules abscesses and neoplastic like formations

Microscopically (Fig 88) the picture very often resembles tuberculosis A section of skin shows usually an irregular epithelium which is thickened and elevated in parts and thin and depressed in others The surface is covered with a mass of irregular debris made up of blood cells epithelial cells and pyogenic bacteria The horny layer may be lacking in places and markedly hyperkeratotic and penetrating deep into the corium in other areas These hyperplastic extensions contain the miliary abscesses which are so characteristic of blastomycosis *These abscesses are widespread throughout the epithelium* varying in size and number and are made up of epithelial detritus leukocytes some in various stages of degeneration epithelial cells nuclear fragments red blood cells giant cells of the Langhans type in varying number and the budding yeastlike cells of the causative organism *Zymonema dermatitidis* The abscesses are surrounded by flattened apparently functionless epithelial cells which form a type of nest The rete is usually edematous infiltrated with leukocytes with its cells enlarged A tuberculoid appearance is presented by cornified cells either as isolated forms grouped or in whorls whereas the aforementioned giant cells occasionally surrounded by a few leukocytes may be seen isolated in the epithelium

The corium also reveals the type of abscesses seen in the epithelium This portion of the skin shows inflammatory changes which may be subacute acute or chronic The infiltrate which is apparently perivascular with the vessels themselves hyperplastic is made up of leukocytes plasma cells and young connective tissue cells varying in density Mast cells and giant cells may also be found sometimes varying in character and in amount Plasma cells giant cells and new connective tissue cells may occasionally show a hyaline degeneration and densely infiltrated areas show a complete destruction of the collagen of the corium The tubercle like formation here too may be seen occasionally

SYMPTOMATOLOGY

Blastomycosis presents numerous clinical manifestations Spreading as it does the disease may be found in practically every organ of the human body Clinically the condition has lesions which are alike both for the *cutaneous* type of the disease or for the *systemic* type with foci in the lungs bones meninges liver and other structures The work of Jacobson in the clinical classification of Gilchrist s disease has been outstanding Accordingly we find that the *cutaneous* (Fig 89) type may be further separated the *primary* beginning in the epidermic layers and the *secondary* when it follows an infection of the deeper tissues viscera and bony structures

The *primary* form of cutaneous or cutis infection may present one of three varied appearances papulo-ulcerative verrucous or papillomatous and gummatous

A B

Fig 87 A Budding cells of *Zymonema dermatitidis* in abscess B Budding cells of *Zymonema dermatitidis* in sputum

Fig 88 Section through cutaneous blastomycosis Note granulomatous response

which give off a purulent or sanguinopurulent discharge from a soft granulating floor Some may develop crusts with raised edges while some may exhibit hyperplastic features with papillomatous characteristics Usually there is a metastatic action on the part of the ulcers represented by the formation of new lesions which are surrounded by a dark red or purplish zone Healing may be spontaneous with indurated scars or infection may persist but may finally yield to treatment with iodides

A study of the ulcers formed in blastomycosis shows them to originate in abscesses which from a clinical point of view can be divided into the *superficial* and *deep* types Secondary cutaneous superficial ulcers arise as a *rule in the* subcutaneous tissues as nodules of varying size These nodules usually enlarge rupture and spread the material over the surface of the skin In some cases they *have* been found to *regress* completely

The deep type of secondary cutaneous blastomycosis characterized by ulcers *smaller in* number and more *deeply* seated is by far the more *serious* destroying bone muscle deep tissues and organs It rarely is erythematous but can be distinguished by the purulent character of the abscesses as contrasted with the mucoid or mucopurulent nature of the superficial abscesses

Practically every organ in the body has been affected as shown either in *living or autopsied material There is however a difference in frequency with* which the various organs are susceptible In the skin and its appendages the infection usually shows the greatest incidence and depree of chance Many skin lesions are manifestations of spreading of the disease from some internal organ The pulmonary system is next in order being followed by kidneys spleen bones and joints liver pleura lymph glands cerebrospinal system vertebrae prostate heart pancreas peritoneum eyes larynx and trachea gastrointestinal tract and the tongue

DIAGNOSIS

In its cutaneous manifestations blastomyco is should be differentiated from tuberculosis verrucosa cutis syphilis neoplasms bromide and iodide eruptions and various *mycotic granulomata* The use of the fungous *extract* blastomycetin has been recommended for diagnostic purposes It is always best however to demonstrate the fungus in tissue pus exudate or sputum or better still by cultivation Diagnostic features are presented in Table VIII

PROGNOSIS AND TREATMENT

Primary cutaneous blastomycosis responds readily to appropriate treatment but scarring usually results *Secondary cutaneous* blastomycosis usually the result of systemic invasion and systemic blastomycosis carry a poor prognosis and unless treated early the latter is fatal

For primary cutaneous blastomycosis the treatment of choice is early destruction of the lesion This can be done locally by surgical excision if the lesion is small Actual cautery electrocoagulation or freezing by solid carbon dioxide may be substituted Potassium iodide by mouth as in moniliasis or

The *papulo ulcerative* type is designated by Jacobson as exhibiting initial lesions which are papulopustular and originate in the epidermis These rupture and discharge the purulent exudate on the surface of the skin with the



FIG 89 Blastomycosis with central atrophy and scar formation

ultimate formation of crusts The process may be proliferative and extend widely roundabout The lesions usually have a violaceous border whose infiltrations regress leaving scarring and atrophy

The *verrucous* or *papillomatous* type is nodular or papular and present on a normal or deep red infiltrated skin Several of the lesions may coalesce to form papillomatous patches which resemble verrucous tuberculosis The lesions may break up into healing areas which upon drying present irregular scars

The *gummatous* type develops from the subcutaneous layers of the cutis in the form of small slightly elevated somewhat tender reddish deep-seated soft nodules situated on the characteristic violaceous red surface of the skin The erythema spreads diffusely followed by the establishment of new nodules in the vicinity The nodules enlarge become soft and gummatous and finally break down to form masses of ulcerative proliferative materials bordered as in the other two types They contain numerous abscesses

The *secondary* cutaneous form consists chiefly of variously shaped ulcers

Eu ope n bla tomycos (Bu se B schk s d sease 894)	C yptococ s hom At lo ha omy es hom n (To ulops n oforman)	S m l In ally t G l ch i c disease but ul rat e type common n cutane u form w th abscesse l ttl nflammation usu lly found nvad ng e e bros nal syst m	Th k w ll d h a aly n apsulat d impl or budd ng lls approximat ly 5– 0µ n diamet r occa onally l rge u ally pp x imat ly 8µ	Colon es) asty o pa ty mooth mu o d to moist ubpuls nate colo light cream be om ng l ght tan to brown with age growth fat	Sph al to o oid bud ding encapsulat d cells app oximat ly 2–6µ in d am ter rarely larg r no my celium pseudomyce lium r pores
So th American bl to mycos P c ccid dal g anu loma (Lutz Splendore de Al me da d sease 9 8) A G n al d type B Local d type aff ct ng the bu cal muco a	( ) P occidioides bras lien.i (b) Pa a occ d o d s tenu s ( ) Paracocc d o de e eb fo mis	A Gen ral ed o local z d utaneou or syst m c granulo matou papulous ver ru ous o ulcerative acute to hron usu ally lymphangit c in pread B Les ons local d on buccal mucosa cute to h on c v rru ous papillomatous ulcer ati g anul matos lymphangit pread only in term nal stage	( ) and (b) Cell spheri cal or ovo d –30µ in diamete arely la g r w th th ck wall s mple or mul t ple budd ng of mi nut phe al o oid or bacill ry gemmule of app oximately 1µ and large ( ) Cell sph al o o oid 3 30µ n di amete rar ly la ger but un formly larger than tho e of I bras li ensis or P tenu s th ck walled with s mple or multiple budd ng of small phe ical o o d o elongated gemmule of approx mately 3µ or o cell oft n found in g ant mac ophages (pseudococcidio d s)	( ) Wh te adh r nt to subst atum and o n what hard w ll de fin d som hat cot tony colon be ome l ght tan with age growth slo (b) Mycelium mostly subm ged colon es compact verrucoid o ermiculate at nocula tion showing fold or rad at ng ridges wh te becom ng light tan with age growth lo ( ) On aga cerebr fo m t s m ulate yea t l ke creamy buff be com ng light c nna mon buff th age a ly sepa ated from sul tratum but fila mentous flat and ad herent to dry port ons of substratum growth lo	( ) Hyphae septate branch ng 1 5 3 5µ hyphal swell ngs 3–5µ spl er cal terminal hlamydospores 1 p to 15µ ntercala y chlamydospo es 6– 0µ irregular scle otic ntercalary c lls 7 X 15µ con d a lat al sess le o pedicel late 3– µ (b) Same as P bras lien s s exc pt that cor re pond ng structures are small r ( ) Hyphae irregular septate b anching 2–7µ in diameter with many swellings cells arth osporous o d o d dumbbell shaped chlamydo por s spl er al elongate pyr fo m or sclerot c nter calary lateral or t r minal up to 15µ co n d a lateral spl er cal or pyriform 3–10µ

8

*Moore M A h Derm 1 & Syph 38 163 190 938

TABLE VIII

CLINICAL AND MYCOLOGIC DIFFERENTIATION OF COCCIDIOIDAL GRANULOMA, BLASTOMYCOSIS, AND PARACOCCIDIOIDAL GRANULOMA (NORTH AMERICAN, SOUTH AMERICAN AND EUROPEAN)

DISEASE	FUNGUS	CLINICAL CHARACTERISTICS	ORGANISMS IN TISSUE OR IN PUS	GROSS CULTURES	MICROSCOPIC CULTURAL APPEARANCE
Coccidioidal granuloma (Posadas disease 1892) (Rixford and Gilchrist 1894)	Coccidioides immitis	Infectious granuloma acute, subacute or chronic, protean, with lesions either cutaneous, subcutaneous or systemic, involving generally the respiratory system; lesions may be nodular, ulcerative, papillomatous, verrucoid, resembling a gummatous tumor or a cold abscess	Cells isolated or in giant cells, spherical, thick walled, with a reported diameter of approximately 2–80μ; reproduces by endospore formation (ascus); budding absent; wall of ascus often showing radiate formation	Colonies flat, somewhat submerged, grayish, becoming white to light cream, with aerial hyphae cottony, at times coremioid; color changes to light chamois and to smoky brown with age; growth rapid	Hyphae septate, branching, 0.5–4μ in diameter; hyphal swellings; arthrosporous cells 2.5–7μ in diameter, 5–12μ in long axis; chlamydospores abundant, 5–8μ in diameter; racquet mycelium; terminal hypnospores approximately 5 × 8μ; endogenous spore formation in anaerobic conditions
North American blastomycosis (Gilchrist's disease 1894)	Zymonema dermatitidis Zymonema capsulatum Zymonema capsulatum var. Isabellinus	Infectious condition, often granulomatous, acute to chronic, protean, with lesions cutaneous or systemic; cutaneous lesions primary or secondary, papulo-ulcerative, verrucous or papillomatous, gummatous, showing typical violaceous color	Simple or budding yeast-like cells, thick walled, approximately 5–20μ in diameter, usually approximately 7μ	Colonies in general at first yeastlike, then prickly (coremioid), finally profuse and cottony, changing from white to chamois, then to cinnamon and to brown, showing radiating ridges and concentric rings of growth; Z. capsulatum remains white and var. Isabellinus a light h mo growth ap d	Hyphae septate, branching, 2–4μ in diameter; conidia pyriform or round, pedicellate or sessile, 5μ in diameter; racquet mycelium 5–6 × 3.5μ; chlamydospores terminal or lateral 5.5–7.5 × 12–15μ, or spherical 7μ n d amet r a og eno s cells sphe al 8– 3μ n d a n t

EPIDEMIOLOGY AND GEOGRAPHICAL DISTRIBUTION

Like Gilchrist s disease this cryptococcosis is not epidemic. It is prevalent in Europe North and South America and no doubt elsewhere as well

PATHOLOGY

This cryptococcosis varies little from Gilchrist s disease except perhaps in the fact that the latter disease is more suppurative or ulcerative Microscopically the lesions of the lungs consist of small miliary nodules or tubercles extending up to 1 cm in diameter with very few or no polymorphonuclear leukocytes Cutaneous lesions are granulomatous in character There is very little congestion but usually areas of *hyalinization or clear zones Within these* areas (perhaps abscesses) the organism may be seen extracellularly or intracellularly In older lesions the fungus is not easily found but the areas of hyalinization or at times of caseation are easily discernible

SYMPTOMATOLOGY

Clinically this disease is divided into the *cutaneous* and *systemic types* The ulcerative type of lesion is predominant in the cutaneous form and microscopically shows abscesses with few leukocytes and little erythema

In North and South America the condition is called torulosis as well as cryptococcosis (Fig 90) Here although the organism is apparently the same it seems to have greater invasiveness and a special affinity for the cerebrospinal *system primarily the pulmonary system being either primarily or secondarily* affected Other organs and tissues have also been involved in the infectious process The skin has been affected on occasion and here the tissue response is similar to that of the European disease

DIAGNOSIS

Like Gilchrist s disease the organism must be found either in tissue sputum *spinal fluid or in skin scrapings to establish a diagnosis* Table VIII is illustrative

PROGNOSIS AND TREATMENT

Cutaneous cryptococcosis carries a prognosis similar to that of North American blastomycosis Pulmonary and cerebrospinal involvement are almost invariably fatal Therapeutic measures are similar to those for Gilchrist s disease

SOUTH AMERICAN BLASTOMYCOSIS

ETIOLOGY

Paracoccidioidal granuloma (paracoccidioidal granuloma or Lutz Splendore de Almeida Disease) is caused by several species of the *genus Paracoccidioides* de Almeida *P brasiliensis* (Splendore) de Almeida 1930 *P tenuis* Moore 1938 *P cerebriformis* Moore 1935

In tissue or pus *P brasiliensis* and *P tenuis* appear as spherical or ovoid

sporotrichosis should be given both as a possible therapeutic and prophylactic measure Roentgen rays applied locally in semi intensive or intensive dosage filtered should be used when lesions are too large for other physical means of destruction

In systemic blastomycosis iodides may be used and accompanied by deep roentgen ray therapy but iodides are contraindicated in some cases of systemic blastomycosis especially when the patient is allergic to the fungus Their continued use is conducive to the further spread of the disease in a manner similar to that in tuberculosis In these cases Martin and Smith advise de sensitization of the allergic state with a heat killed vaccine and then the administration of treatment

EUROPEAN BLASTOMYCOSIS

ETIOLOGY

The cause of European blastomycosis (cryptococcosis torulosis or Busse Buschke s disease) is a yeastlike budding organism which does not produce hyphae even in culture The nomenclature of this fungus has been somewhat confusing Busse referred to a *Saccharomyces hominis* which was later named *Cryptococcus hominis* by Vuillemin (1911) Since that time the fungi isolated in Europe have been generally referred to by this latter denomination In 1909 De Beurmann and Gougerot established the genus *Atelosaccharomyces* using Busse Buschke as the species name for the same organism In the United States an organism supposedly similar both morphologically and bio chemically and which produced lesions of the brain and the meninges was named *Torula histolytica* by Stoddard and Cutler This organism is now gen erally referred to as *Cryptococcus histolyticus* In Europe Lodder and Gior dano basing their studies on a comparison of the various known existing yeastlike fungi of this group from the United States and Europe placed the organism in the genus *Torulopsis* Berlèse 1894 and in the species *neoformans* described by Sanfelice in 1895 However it is the usage of today to call this fungus *Cryptococcus hominis* Although the organism of meningitis has a certain invasiveness and is called *C histolyticus* it may also be called *C hominis*

C hominis is seen in the abscesses as a spherical to ovoid simple or budding yeastlike cell which measures from 5 to 10 microns in diameter usually about 8 microns In tissue or in pus the cells of the fungus are surrounded by a *thick mucoid refractile capsule which does not stain by ordinary* methods or if at all lightly

When cultured the colonies are yeasty or pasty smooth mucoid to moist and somewhat varied in appearance The color is light cream becoming light tan to brown with age Microscopically the cells are spherical to ovoid and budding They have a thick wall and a thin capsule in young cultures The latter are definitely apparent in old cultures particularly in carbohydrate media They measure approximately [illegible] to 6 microns in diameter and exhibit no mycelium pseudomycelium or spores that is they are definitely smaller in culture than in tissue

cells 1 to 30 microns in diameter rarely larger with thick walls They exhibit simple or multiple budding in the form of exceedingly minute spherical ovoid or bacillary gemmules approximately 1 micron or larger in diameter



Fig 9 P o d d b a l en is in giant cell

P cerebriformis shows spherical or ovoid cells 3 to 30 microns in diameter rarely larger but uniformly larger than those of *P brasiliensis* or *P tenuis* Their gemmules are approximately 3 microns or more in diameter They often occur in giant macrophages (pseudococcidioides) (Fig 91)

Macroscopically the cultures of *P brasiliensis* have a white cottony surface They are adherent to the substratum and somewhat hard and well defined The colonies become light tan with age With *P tenuis* the mycelium is mostly submerged the colonies being compact verrucoid or vermiculate at the inoculation point with peripheral folds or radiating ridges The color is white becoming light tan with age *P cerebriformis* develops on agar a cerebriform or vermiculate yeastlike creamy buff colony which becomes light cinnamon buff with age The culture is easily separated from the substratum but is filamentous flat and adherent to the dry portion of the culture medium

Microscopically the hyphae of *P brasiliensis* are septate and branching They measure from 1 2 to 3 4 microns Hyphal swellings 3 to 5 mi

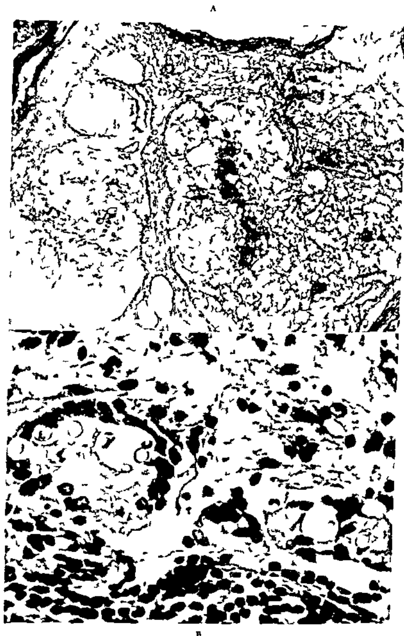


Fig 90 A Section through lesion of cutaneous cryptococcosis Note absence of leukocytic response (Mook and Moore 1936)
B Cryptococcosis of brain Note encapsulated organisms in giant cells (Courtesy of Department of Pathology Washington University School of Medicine)

tacked primarily with acute ulceration and inflammation and localized lymphangitis which soon becomes generalized This constitutes the fully developed typical granulomatous acute blastomycosis

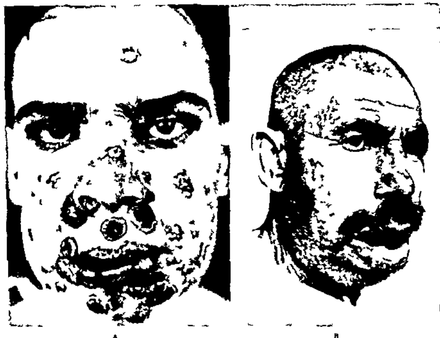


FIG 92 A. Cutaneous paracoccid o dal granulom —frambes form type (Co rtesy of Dr J de Aguiar Pupo)
B Local zed buccal mucosa type of paracoccid o d l granuloma

A fourth clinical type may be regarded as the *mixed type* (Fig 92) In this the systemic involvement is accompanied by the cutaneous lesions which manifest themselves in the following forms (1) *papular* the lesions being superficial and lenticular at first but tending to develop into superficial ulcers and epidermic micro-abscesses (2) *papulopustular* localized in follicles (3) *tuberous* made up of small nodules which infiltrate the dermis (4) *ecthymiform ulcerating* lesions (5) *vegetative* types papillomatous exudative lesions covered with a serous or seropurulent crust (6) *hypodermic granuloma* nodular in type forming subcutaneous absces es with secondary ulceration (7) *scrofulodermic* exhibiting cutaneous abscesses and fistulae In addition the lesions of the mouth and lips give rise to (8) *mulberry type of ulcerous stomatitis* with the lesions localized in the buccopharyngeal mucosa The moruloid lesions begin at the edge of the gums and extend to the floor of the mouth and related parts (9) *hypertrophic diffuse granuloma of the lips* with a tendency to ulcerate and showing the same order of mulberry like formation

crons spherical terminal *chlamydospores up to 15 microns intercalary* chlamydospores 6 to 10 microns irregular sclerotic intercalary cells 7 by 15 microns conidia lateral sessile or pedicellate 3 to 7 microns *Paracoccidioides tenuis* shows a similar morphology except that the corresponding structures are smaller *Paracoccidioides cerebriformis* has irregular septate branching hyphae 2 to 7 microns in diameter with many swellings Its cells may be arthrosporous oidioid or dumbbell shaped Chlamydospores are spherical elongate pyriform or sclerotic intercalary lateral or terminal and measure up to 15 microns Lateral conidia are spherical or pyriform and measure 3 to 10 microns

EPIDEMIOLOGY AND GEOGRAPHICAL DISTRIBUTION

Like North American and European blastomycosis paracoccidioidal granuloma is not an epidemic disease It is prevalent throughout South America especially in Brazil Uruguay and Argentina and occasionally appears in the other countries It is present in the rural districts being especially prevalent among the coffee farm workers

PATHOLOGY

Tissue reactions are similar to those occurring in Gilchrist s disease Papules vegetative formations pustules ulcerations tuberculoid manifestations and frambesiform lesions are seen Giant cell formation and infiltration with lymphocytes plasma cells and leukocytes are noticed microscopically in addition to other granulomatous changes

SYMPTOMATOLOGY

Clinically paracoccidioidal granuloma may be divided into the *localized buccal mucosa* type due to *Paracoccidioides cerebriformis* and the *generalized* form due to *P brasiliensis* and *P tenuis* The generalized form may be acute or chronic The fungus may enter the buccal cavity lodging usually in the gums and forming a hard infiltration which spreads to the lips the nose and the margin of the tongue Histologically this presents the picture of granuloma A pseudotuberculous papule may be produced on the uvula and a papillomatous vegetation may develop on the tonsils and the gingiva giving the appearance of an acuminate condyloma The ulcerative processes may spread to the skin presenting likewise vegetative and papillomatous lesions on the body In generalized cutaneous infections of the skin (*cutaneous type*) the primary lesions may have developed as the result of an abrasion or wound

The lesions of many cases of chronic paracoccidioidal granuloma may remain localized in the mouth The invading germ however may penetrate into the tonsils causing the disease to become systemic by way of the *lymph stream* This leads either to the *lymphangitic type* affecting the glands of the neck supraclavicular region and axillae and often simulating Hodgkin s disease or the *visceral type* affecting the internal organs When *P cerebriformis* is the causative agent lymphangitis usually occurs in the terminal stages of the disease Where *P brasiliensis* or *P tenuis* are concerned the tonsils may be at

PATHOLOGY

The reaction of the tissue is similar to that seen in other mycotic granulomata particularly blastomycosis Microscopically the skin shows acanthosis and

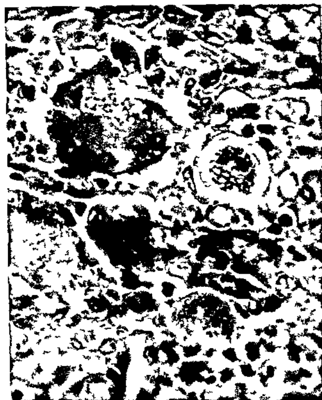


Fig 93 *Coccid oides im* t in t ssu

marked parenchymatous or interstitial edema with some vesicles in the epidermis The abscesses which form never attain the size of those seen in blastomycosis The nodular type of lesion usually suppurates and becomes necrotic but rarely forms definite abscesses The cutis shows a granulomatous reaction with an infiltration and proliferation of lymphocytes plasma epithelioid and giant cells the latter of the Langhans type There is also seen the formation of new blood vessels A tuberculoid response is evidenced by the formation of tubercles surrounded by epithelioid plasma and lymphoid cells the tubercles may show caseation and liquefaction necrosis and eventually fibrosis and calcification The edema in the epidermis may extend into the corium and subcutaneous tissue while in various skin lesions there is marked hyperplasia in the epidermis accompanied by whorl and pearl formation resembling a carcinomatous process

DIAGNOSIS

The finding of the characteristic organisms is important since this disease may simulate other mycotic granulomata syphilis tuberculosis and neoplasm (Table VIII)

PROGNOSIS AND TREATMENT

The prognosis and treatment is similar to that for the other blastomycoses

COCCIDIOIDAL GRANULOMA

Coccidioidal granuloma (coccidioidomycosis California disease valley fever Posadas disease dust fever or dermatitis coccidioides) is an infectious condition caused by *Coccidioides immitis*

ETIOLOGY

When seen in tissue or pus *Coccidioides immitis* (Fig 93) Stiles 1896 may be found either isolated or within giant cells as a spherical thick walled structure with a reported diameter of approximately • to 80 microns It reproduces by endospore formation and shows no budding The wall of the mother cell may often show radiate formation

Cultures develop as flat somewhat submerged colonies grayish in color becoming white to light cream and changing to light chamois or smoky brown with age The surface mycelium is aerial cottony and somewhat coremioid

Microscopically the cultured organism shows branching septate hyphae *0 5 to 4 microns in diameter with hyphal swellings and arthrosporous cells 2 5* to 7 microns in diameter and 5 to 1• microns in the long axis There are numerous chlamydospores 5 to 8 microns in diameter with racquet mycelium and terminal hypnospores approximately 5 by 8 microns Endogenous spore formation takes place in anaerobic to partially aerobic conditions

EPIDEMIOLOGY AND GEOGRAPHICAL DISTRIBUTION

Coccidioidal granuloma has been reported as causing small epidemics among soil workers and cattle handlers The disease is endemic in certain areas of the United States especially in the San Joaquin Valley where the climate is unusually hot and dry It has also been described from other parts of the United States and from Argentina The organism has been isolated from the soil and from cattle sheep rodents and dogs

Numerous workers have demonstrated the entrance of the organisms through an abrasion or other wound in the skin Because of its frequent occurrence in hot climates the pulmonary type of infection is common due to the inhalation of spores It is probable indeed that such clinical types as involve the meninges subcutis bones and joints are primarily pulmonary infections The pulmonary involvement may not be recognized at first but postmortem examinations usually demonstrate it in such cases

losis Those of bone infections can hardly be differentiated from osseous tuberculosis osteomyelitis or arthritis Involvement of the meninges and spinal cord simulates closely tuberculous meningitis epidemic meningitis



Fig 94 Coccidioidal granuloma—cu t neous fo m (After Jacobson)

and tumors of the spinal cord Gastro intestinal disorders of coccidioidal granuloma usually run the typical course of typhoid fever and not until secondary cutaneous lesions develop is an accurate diagnosis usually made Lymph node involvement usually suggests lymphatic leukemia Hodgkin s disease and lymphosarcoma

Pulmonary coccidioidal granuloma in its early stages simulates a cold with a chill followed by headache fever pain in the chest bones and joints and finally a cough which becomes productive and often blood streaked The

In the lungs the lesions may be similar grossly to those of miliary bronchopneumonia or bronchiolitis miliary tuberculosis (acute or chronic) miliary carcinomatosis secondary stage silicosis they may produce induration cavitation and caseation The disease is less marked in the region of the mediastinum *than in the periphery of the lung field Lesions are usually absent in the* esophagus and small intestine Microscopically the reaction is similar to that seen in the skin with marked edema infiltration and proliferation of the various cells necrosis tubercle formation some caseation and liquefaction and finally fibrosis and calcification

SYMPTOMATOLOGY

A form of acute pulmonary involvement called valley fever desert fever or coccidioidomycosis has been recently shown by Dickson and by others to be due to *Coccidioides immitis* Approximately nine days following exposure the influenza like symptoms appear accompanied by erythema nodosum Most patients recover from this acute type without complications but in some instances the disease progresses into the granulomatous form (coccidioidal granuloma) (Fig 94)

Coccidioidal granuloma may be exceedingly acute and end fatally in a few weeks or it may be chronic and painful extending over several years On the other hand it may be long drawn out and attended with little pain There is a third or subacute type which is characterized by a definite tendency to wide spread dissemination With this form remissions and relapses are associated the sufferer living from six months to two years

Clinically coccidioidal granuloma is a localized or systemic disease granulomatous in nature and protean in its expressions often simulating tuberculosis syphilis granulomatous mycotic infections and neoplasms The disease may manifest itself in one of several types

(1) Primary cutaneous lesions followed by generalization

(2) Primary pulmonary lesions followed by generalization but without cutaneous lesions

(3) Primary pulmonary lesions and secondary subcutaneous lesions

(4) Primary pelvic meningeal or spinal cord or joint involvement with no cutaneous lesions

(5) Primary bone or subcutaneous lesions with secondary cutaneous lesions

The multiform clinical expressions of this condition are referable in the final analysis to proliferative and suppurative processes as typified by the verrucoid dermic lesion Fundamentally dermic lesions are nodular and ulcerative The ulcers are painless deep seated pinkish to dusky red becoming necrotic and sluggish and they may develop papillomatous growths They thus resemble epitheliomas warts tuberculosis in its various forms syphilis blastomycosis or even sporotrichosis Subcutaneous involvement is represented by three types of lesions flaccid tumor abscess and gummatous structures these may imitate cold abscesses or tumors as the names imply

The symptoms in pulmonary infections resemble closely pulmonary tubercu

at the pore (Fig 93) and the spores are liberated either into the nasal cavity or into the lymphatics The spores are distributed in the connective tissue by means of the lymph where they become localized and repeat the cycle

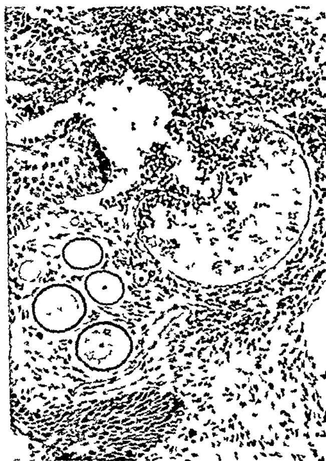


Fig ; Forms of Rhinosporidium s beri in tissue

EPIDEMIOLOGY AND GEOGRAPHICAL DISTRIBUTION

Although there is certain evidence of infection from man to man it is not generally believed that the disease is contagious or epidemic It is particularly prevalent among sand workers and water divers Karunaratne lists ca es from India Ceylon England Scotland Malay States Philippines United States Argentina Paraguay Uruguay Italy and South Africa These ca es have oc curred among white peoples Negroes Zulus Eurasians Chinese Filipinos Singhalese Ceylon Tamils Indian Tamils Moors Malayans and Malayalees The age incidence varied from five to eighty four years of age

patient shows a loss of weight night sweats and gastro intestinal disorders As the disease process continues and the organisms increase in number setting up more foci of infection the symptoms become aggravated and death results in a short time

DIAGNOSIS

Coccidioidal granuloma may resemble many other diseases as has been described As a diagnostic test Hurwitz Young and Eddie and Kessel (also Stewart) advocate the use of coccidioidin—the fungous extract Kessel believes it to be specific for coccidioidomycosis The finding of the organism establishes an unquestionable diagnosis (Table VIII)

PROGNOSIS AND TREATMENT

Early acute coccidioidal granuloma (valley fever) usually clears spontaneously Primary cutaneous lesions without systemic involvement are amenable to surgical treatment Chronic pulmonary and cerebrospinal forms are invariably fatal

The treatment of coccidioidal granuloma depends largely on the extent of the lesions Potassium iodide volatile oils and their derivatives and arsenicals have been found wanting Colloidal copper intramuscularly according to Jacobson and 1 per cent antimony potassium tartrate intravenously according to Lewis and Hopper have given encouraging results Roentgen ray therapy is valuable only in a palliative way Thymol in doses of as much as 6 grains daily has helped a patient Sulfanilamide may be of valuable assistance Coccidioidin is said to have helped in some instances

RHINOSPORIDIOSIS

Rhinosporidiosis is a chronic disease characterized by the formation of polyps on the nasal and other mucosa and papillomatous vegetations on the skin It is caused by *Rhinosporidium seeberi*

ETIOLOGY

The causative organism is *Rhinosporidium seeberi* (Wernicke) Seeber 191 It was originally named *Coccidium seeberi* by Wernicke in 1900 and *Rhinosporidium kinealyi* by Minchin and Famtham in 1905 It has not been cultivated In tissue the organism appears first as a small cyst aproximately 6 microns in diameter *with a chitinous wall vacuolated cytoplasm* a vesicular nucleus and a karyosome The cell enlarges and when it reaches a size of 50 to 60 microns mitosis occurs showing four chromosomes Synchronous division or mitosis continues and at about the seventh division when the cell is approximately 100 microns in diameter and has about 1-8 nuclei the wall becomes thickened except at one point the future pore When the number of nuclei is about 4 000—the twelfth synchronous division—the cytoplasm divides twice and breaks up into rounded masses These form the spores which round up and appear as refringent spherical to ovoid spherules The mother cell ruptures

cattle There are supposedly two distinct groups of organisms (1) that which invades human tissues and which is supposed to be anaerobic (micro-aerophilic) and is termed *Actinomyces bovis* or as Negroni prefers *A israeli* based on the



Fig 96 Actinomycotic granule in tissue

work of Wolff and Israel and (2) that found on grasses and other vegetation called *Actinomyces* of Bostroem and which is aerobic In the latter numerous pleomorphic bodies resembling micrococci are present in the tissue granules

The *Actinomyces* vary greatly in pathogenic power They frequently appear in the sputum without any pathologic significance or as secondary invaders usually in significant diseases such as tuberculosis Aerobic strains may be isolated from the soil However aerobic strains may also be isolated from human infections *On the other hand many strains of Actinomyces have been isolated* from dental and tonsillar crypts both aerobic and micro-aerophilic Since actinomycosis usually occurs at a site of trauma the prevailing theory is that the organism is brought in from the outside usually on some foreign material The second theory is that because of its presence in the mouth it is able to produce infections as an opportunist

A prominent characteristic of *Actinomyces* (Fig 96) in tissue is the forma

PATHOLOGY

The polyps or pedunculated masses show branching strands of fibrous tissue among which pin head sized cysts are scattered The mucosa is folded to form papillomatous projections The subepithelial tissue is edematous showing an infiltrate of polymorphonuclear leukocytes lymphocytes plasma cells and eosinophiles The infected tissue shows numerous spore filled sacs measuring from 6 to 300 microns some of which seem to be pushing out from the mucosal surface

SYMPTOMATOLOGY

The attention of the patient is first drawn to the infection by frequent bleeding at the site The lesion starts as a small freely moving pedunculated nodule the size of a pea They are usually painless and are attached in most cases to the anterior and upper part of the cartilaginous septum Masses then develop to form pedunculated or sessile strawberry or mulberry like tumors or papillomata *These show closely packed tendrils suggestive of villous polypi* or filiform verrucae There is much in favor of the theory that they form at the site of trauma

Sites of the lesion as reported in the literature are chiefly the nose nasopharynx uvula conjunctiva lacrimal sac soft palate penis vagina ear larynx and skin

On the skin the lesions appear as large malodorous fungating easily bleeding tumor like masses

DIAGNOSIS

Diagnosis is usually made by finding *R seeberi* in biopsy material

PROGNOSIS AND TREATMENT

The prognosis is generally good but the condition may recur and on occasion may spread to produce a generalized infection with a fatal outcome The best treatment is to remove the infected mass by excision followed by cauterization

ACTINOMYCOSIS

Actinomycosis or lumpy jaw is a local or systemic disease granulomatous in nature and may be acute subacute or chronic It is characterized chiefly by sinuses and fistulae from which may be isolated variously colored granules which are largely masses of mycelium of certain species of the genus *Actinomyces* There are various synonyms for *Actinomyces* These include *Nocardia Discomyces Streptothrix Actinobacterium Cohnistreptothrix Brevistreptothrix* and *Proactinomyces*

ETIOLOGY

The *Actinomyces* are classed both as low fungi or as high bacteria and have been known under a number of names In 1877 Harz created the genus *Actinomyces* and the species *bovis* to indicate the organism obtained from

in size the fungous elements become intertwined and compact to form the granules and the pus burrows peripherally Eroding through soft tissue and even bone the organism and pus eventually reach the surface of the skin re



A B

Fig 97 A Actinomycosis of face B Actinomycosis of leg following surgical n i on

sulting in sinuses The latter do not heal they intercommunicate with fellow sinuses and at times large abscess cavities form along the pathways The tissue affected is thus made up of sinuses abscess cavities and masses of granulation tissue in which the granules may be found in varying numbers

SYMPTOMATOLOGY

Clinically actinomycosis can be divided into two main groups *cutaneous* and *visceral*

The cutaneous type may be either *primary* occurring in the epidermic layers as a nodule which extends into the corium and subcutaneous layers or *secondary* to a deep seated infection which usually occurs in the tissues closely associated with the buccal thoracic or abdominal cavities and which pushes its way to the superficial layers of the skin

In primary actinomycosis of the skin (Fig 97) the nodule penetrates into the deeper layers of the skin enlarges softens at the surface becomes fluctuant and finally ruptures exuding a seropurulent or sanguineous material containing the so-called sulfur granules The nodule ulcerates and eventually becomes scarred or forms a crust Often new nodules form in the vicinity of the first nodule these going through the same type of evolution The lesions change in color from pink to dusky red

tion of granules These are found in four colors whitish to whitish yellow black green or red

There are numerous species of *Actinomyces* The most common is *A bovis* (*A israeli*) Another common pathogen is *A asteroides* which has been isolated from the brain and which grows aerobically

The fungus in tissue may be seen in its early stage as a bacillus then as a fine usually non septate occasionally branching filament measuring approximately 0 ? to 0 6 micron in diameter and varying in length but approximately 15 microns As the fungus colony enlarges it amounts to a granule the so-called ray fungus At this time the stained granule is made up of a central area of intertwining mycelial filaments with pigment granules and leukocytes This is surrounded by a deeply stained more or less amorphous area and finally the periphery may show the so called clubs appearing as a radiating fringe of fine broadened projections The clubs are the growing portion of the filaments which are filled with metachromatic material

The type species of the genus *Actinomyces* is *A bovis* Since there are a number of species involved the description of this organism will serve as a guiding mark Most of the species can be cultured aerobically some however can be grown only under anaerobic conditions On synthetic agar the growth *is somewhat restricted with yellowish aerial mycelium appearing late* and becoming light sulfur yellow and powdery On potato growth is abundant wrinkled and the color gray to canary yellow The hyphae are slender branched approximately 1 micron in diameter usually less but never more than 1 5 microns Septa if present are clearly discernible The conidia are borne on specialized conidiophores usually in coiled chains which break very easily and therefore are not easily found

EPIDEMIOLOGY AND GEOGRAPHICAL DISTRIBUTION

There seems to be no evidence that actinomycosis is epidemic or that the disease spreads from man to man Lesions are usually spontaneous In many cases they are found among workers of the soil and cattlemen Usually they are found at a site of trauma or presumably as a result of the chewing of infected foods or straws On the other hand the theory of *locus minoris resistanciae* based on the more or less continuous presence of the fungi in the mouth could hold true in a number of cases

The disease is present throughout the world

PATHOLOGY

Microscopically the lesion is granulomatous presenting a picture which could at times be mistaken for tuberculosis syphilis or some other mycotic granulomata The typical lesion however consists in its early stages of a central area of polymorphonuclear leukocytes and fungous elements Cellular debris and cells in various stages of degeneration are interspersed in this central area usually surrounding it Surrounding this mass there is an area of granulation tissue As the central pyogenic mass or so-called abscess increases

have given a good result in some cases Roentgen ray therapy has been used with success in localized cases but is of little or no value in systemic involvement Surgical drainage is based on the supposition that the organism is anaerobic and that the entrance of air following the free opening of the many sinus tracts and the resection of the diseased tissue may bring about a cure However surgery unless wisely applied may cause a spread of the organisms with resultant multiple foci of infection Iodine beginning with 5 drops three times a day and increased to tolerance and copper sulphate 1/4 grain doses by mouth have been used with reported success Thymol 1 to 2 gm daily by mouth on an empty stomach or 10 to 20 per cent in olive oil applied locally or injected into the sinuses have given beneficial results Sulfanilamide given orally 15 grains three times a day or 0 75 gm every four hours has given beneficial results as reported by Walker and by Dobson Holman and Cutting Vaccines have been used successfully by Colebrook and in 33 per cent of the cases treated by Negroni

MADUROMYCOSIS

Maduromycosis (mycetoma madura foot) is a chronic granulomatous infectious process localized usually in the extremities (Fig 98) but occasionally affecting other parts of the body It is characterized by variously sized enlargements of the cutaneous surface or even entire body parts which eventually give rise to intercommunicating sinuses and fistulae from which variously colored granules comprising fungous elements of the genera *Actinomyces Madurella Monosporium Trichosporium Aleurisma Allescheria Indiella Aspergillus Penicillium* and *Sterigmatocystis* can be obtained

ETIOLOGY

Maduromycosis like actinomycosis is characterized by its variously colored granules which are due to different fungi These have been adequately described by Gammel and by Brumpt Briefly they are (1) black granules—*Madurella Glenospora Torula* (perhaps *Cryptococcus*) *Aspergillus* and *Penicillium* (2) white or yellowish white granules—*Monosporium Indiella Sterigmatocystis Cephalosporium* and *Allescheria* (3) greenish yellow granules —*Aspergillus* and (4) red granules—*Aspergillus* and *Rubromadurella* The genus *Actinomyces* likewise may cause lesions of mycetoma

The nature of the actinomycotic granule has been referred to under the disease actinomycosis The granules of maduromycosis vary according to the type of fungus involved The young ones are composed of intertwining septate hyphae together with certain spherical cells chlamydospores The mature granules are made up of three distinct zones the central area consists of mycelial elements hyphae and chlamydospores and some pigment granules this is surrounded by a deeply pigmented irregularly amorphous zone the outer zone is acidophilic having fine filamentous prolongations more or less radiate and refractile Dispersed through the granules are leukocytes in various stages of degeneration

Cutaneous lesions secondary to subcutaneous involvement appear as subcutaneous nodules or tumors which are rather firm and livid As they increase in size they soften fluctuate and break down to discharge a seropurulent material containing the granules Sinuses are produced which become intercommunicating and through which the fungi are distributed setting up new foci of infection in the form of nodules The surrounding skin then becomes a mass of granulomatous material covered by an oozing discharge and granulation tissue The picture can become confusing diagnostically and simulates at times carcinoma

In its visceral manifestations actinomycosis may show various anatomic involvements beginning with the tongue extending to the tonsils pulmonary system intestinal tract urinary tract cerebrospinal system and the osseous structures The destructive processes are of the same order as those that occur in the skin nodules are developed which enlarge soften fluctuate and rupture producing sinuses and fistulae often giving rise to large masses The ruptured nodules discharge their material which sets up abscesses throughout the involved tissues Occasionally the fungus bores through the adjacent subcutaneous layers to the surface of the skin and develops intercommunicating fistulae

Four types of pulmonary actinomycosis have been described *bronchitic pneumonic pleuropneumonic* and *metastatic* When the lung parenchyma *is* involved the patient suffers from symptoms resembling bronchopneumonia with leukocytosis high intermittent fever sweating and lassitude

The relative frequency of the three types of cases is as follows

Cervicofacial	60 per cent
Abdominal	20 per cent
Thoracic	10–15 per cent

DIAGNOSIS

Actinomycosis like other mycotic granulomatous diseases may simulate a number of conditions both of mycotic and non mycotic origin The finding of the granules or organisms in the discharge is the best assurance of a correct diagnosis Usually the lesions are diagnostic The use of serum from a patient with the disease for the agglutination of *Actinomyces* has been tried successfully Cutaneous reactions with vaccines have also been tried but not sufficiently to evaluate the technique or results

PROGNOSIS AND TREATMENT

Localized actinomycosis will respond to proper treatment Systemic involvement if not of long duration may likewise show improvement under adequate treatment However prognosis is usually not good once the disease becomes systemic the outcome is fatal in most cases especially if the organism invades the cerebrospinal system and the brain

The treatment of actinomycosis has not been at all satisfactory Iodides

Like the other mycotic granulomata the fungus is not known to be epidemic in nature The organisms grow chiefly as saprophytes in nature and lesions usually develop at a site of trauma especially on the extremities

PATHOLOGY

Grossly maduromycosis appears as large tumefactions of various size and shape The cutaneous surface shows scarring with ulcerating nodules and fistulae over the enlarged swelling The microscopic picture of maduromycosis is distinctly granulomatous with the general picture of active proliferation and infiltration of the various types of cells encountered in other mycotic granulomata together with local necrosis and abscess formation and the eventual formation of fibrous tissue

The process is characterized by the presence of abscesses some of which are still suppurative while others tend to sclerose It is within these that the distinctive granules occur The abscesses may be small and round or they may coalesce and become large irregular or elongate They develop eventually into sinuses which reach the surface of the skin The acute abscess is made up of small and large lymphocytes large mononuclear and polymorphonuclear leukocytes blood cells cellular detritus and albuminoid bodies all in and around the granules Some of the small abscesses are made up predominantly of lymphocytes and plasma cells while others contain multinucleated giant cells surrounded by a thick sclerotic wall The wall of the abscess is made up of an inner layer of connective tissue fibrils or large mononucleated cells more or less spheroidal and vacuolated due to the presence of fats Surrounding this is a second layer comprising granulation tissue well vascularized and then an outer layer of dense connective tissue Eosinophiles have been occasionally observed

SYMPTOMATOLOGY

Maduromycosis as described by Carter was modified by Brumpt and described as mycotic inflammatory tumors which produce granules of varied colors and dimensions formed by an interlacing of the mycelial elements and which are eliminated to the exterior of the tumor through more or less developed fistulae

The lesions whether of the actinomycotic or maduromycotic type give rise to lesions which develop mycetomas as the result of trauma either on the extremities cervicofacial or cephalic, thoracic and abdominal regions The lesions may become manifest first as areas of localized tenderness or pain with slight swelling These then may develop into four types as described by Carter a papule which may be livid or mottled and is neither feverish nor painful a deep seated and fixed nodule a swollen area which becomes hard and develops a vesicle and finally an abscess which ruptures to produce a sinus Usually however the initial lesion is deep-seated with increase in size new lesions appear as satellites As a result there is developed an edema more or less gummatous in nature which takes on the characteristics of a tumor The

When cultured the organisms vary in their gross appearance A species of *Madurella* on Sabouraud s maltose agar after twenty days shows a grayish white irregular periphery with a brown pigment diffusing into the medium



FIG 98 Mycetoma caused by *Actinomyces* (Courtesy of Dr G Ives)

The center of the culture exhibits a brown somewhat irregularly elevated growth with brown drops of watery condensation on the surface *Monosporium* on the other hand shows a growth of compact mycelium which is arranged in sectors The growth at first is white and aerial later it becomes smoky and then cinnamon drab

Microscopically *Madurella* is made up of hyphae measuring 1 5 to 5 microns in diameter with numerous chlamydospores approximately 10 microns in diameter but ranging upward to 15 microns together with sclerotic cells

Monosporium apiospermum shows somewhat branched and septate hyphae 0 5 to 5 microns in diameter with ascending highly attenuate branches terminating in a single conidium Conidia are unicellular pyriform measuring 8 5 to 11 by 5 5 to 7 microns They are sometimes spherical guttulate smooth hyaline becoming amber walled Sclerotia are found both in media and in the tissues of the host

EPIDEMIOLOGY AND GEOGRAPHICAL DISTRIBUTION

Maduromycosis is prevalent throughout the world particularly in hot and dry regions such as occur in the tropics



Fig 99 Chromocycosis of extremity (Brazilian case)



Fig 100 Large sclerotic, multilocular cells seen in lesion of chromomycosis

whole mass increases in size and then begins to soften fluctuate with the primary more superficial lesions rupturing to discharge a characteristic oily seropurulent blood streaked viscid fluid within which are found the typical black yellow white or red granules The sinuses thus formed may or may not heal rapidly usually they persist as the affected part swells producing new lesions which go through the same evolution to form intercommunicating sinuses which discharge the characteristic material

DIAGNOSIS

The differentiation of the mycetomas rests almost entirely on the microscopic examination and mycologic determination of the various granules and the subsequent cultivation and identification of the fungi involved

PROGNOSIS AND TREATMENT

Early lesions if not extensive can be removed entirely and offer a good prognosis since wound healing is fairly rapid and there is no recurrence Extensive lesions involving the bone have a bad prognosis especially if the lymphatics are involved

The usual treatment has been the use of iodides copper sulfate and roentgen radiation Localized lesions if not extensive are best treated by radical surgical removal If extensive amputation with removal of the regional lymph nodes is advised

CHROMOMYCOSIS

Chromomycosis chromoblastomycosis or dermatitis verrucosa cutis is a chronic granulomatous disease involving usually the extremities and rarely other parts of the body The lesions may be papular nodular verrucoid or granulomatous (Fig 99) with or without ulceration and abscess formation Systemic invasion is unknown but rarely the lymph glands are involved Pain or pruritis is rare Thick walled brown multilocular cells of the various genera *Phialophora Hormodendrum Hormodendroides Botrytoides* and *Phialoconidiophora* are found in the tissues or exudate

ETIOLOGY

There are several organisms which may cause chromomycosis The first described in the literature is *Phialophora verrucosa* Thaxter 1915 The organism isolated by Gomes and reported in 19 0 was studied by Brumpt in 1922 and named *Hormodendrum pedrosoi* On the basis of morphologic characteristics Moore and de Almeida separated several of the organisms and created the genera *Hormodendroides Botrytoides* and *Phialoconidiophora* Negroni however preferred the new generic name of *Fonsecaea* All of the organisms seem to be related generically differing by reason of morphologic variation

Microscopically the large sclerotic cells (Fig 100) of the fungus in tissue or pus are dark brown thick walled spherical or irregular in outline single multiple or multilocular approximately 3 to 10 microns in diameter They

The sites of election are the feet the dorsum and sides of the legs extending up to and above the knees the dorsal region of the hands involving the fingers and wrist and extending up to and somewhat above the elbows the buttock and the face ear and neck The infection is usually the result of invasion of a traumatized area

The process commonly starts as a small papule which becomes papillomatous and ulcerates The lesions are usually superficially located in the dermis but may extend down into the subcutaneous tissue even to the muscle where abscesses are produced No osseous or visceral lesions have been known to occur except for lymph gland involvement Adenitis may occur due to secondary bacterial infection

The primary papules and nodules are indolent and reddish in color They become fluctuant but on mechanical rupture exude only a little blood They become verruca like papillomatous raised to a height of 1 cm or less above the surface of the skin They are covered with a yellowish white crust which may be removed painlessly Under the crust is a moist base which on pressure may exude a mucoid serous or purulent material containing the typical fungi The vegetation further shows sessile or pedunculate or psoriasiform lesions The lesion extends peripherally occupying large areas without any tendency toward central healing Subcutaneous lesions may develop forming suppurating nodules which by a process of autoinoculation give rise to new lesions on the adjacent skin

DIAGNOSIS

Chromomycosis may closely resemble tuberculosis verrucosa cutis syphilis carcinoma or other mycotic granulomata In Brazil it is often found associated with leishmaniasis The organism can be easily demonstrated in tissue or in the exudate Complement fixation has been demonstrated by Conant and Martin

PROGNOSIS AND TREATMENT

Chromomycosis is not a fatal disease The lesions may be chronic but have not been found systemically at necropsy There may be limitation of motion as a result of scar formation and stiffening of the joints or incapacitation as a result of the swelling of the extremities

Early lesions have been treated successfully with iodides in some instances Roentgen ray therapy may be of value Locally destruction by cautery or excision may be done but care should be taken to avoid spreading the organisms In chronic elephantiasic like lesions of the extremities amputation has been the only possible means to check the spread of the disease

HISTOPLASMOSIS

Histoplasmosis (Darling s disease or cytomycosis) is an infection of the spleen liver lungs lymph nodes other internal organs and of the skin which is characterized by emaciation anemia leukopenia splenomegaly and fever It is caused by members of the genus *Histoplasma*

reproduce by enlargement and cross wall formation to form mulberry like clusters never by budding In old necrotic lesions there may be seen short filaments which are germinations of the spherical sclerotic cells

Grossly the organisms grow as black colonies the size of a pin head These develop into cultures of various descriptions depending on the type of organism but usually appear as spherical to irregular growths somewhat raised with aerial mycelium with or without ridges excrescences or dendroid appearance the color varies from rat gray dark or light olivaceous green to ochraceous brown or black

Microscopically there are different features depending again on the genus and species of fungus *Phialophora verrucosa* may be described as follows filaments or hyphae septate branching or in moniliform chains 2 to 6 microns in diameter sporogenous cells short ampulliform or more elongate usually terminal or irregularly distributed near the ends of branchlets spores or conidia ovoid to ellipsoid elongate or short 1 to 3 by 2 to 4 microns These conidia occur usually in groups at the mouth of the phialides or cups *and are held together by a mucilaginous material termed gloea Oidioid* cells measure approximately 5 microns in diameter

EPIDEMIOLOGY AND GEOGRAPHICAL DISTRIBUTION

Chromomycosis is not an epidemic disease Lesions are found at a site of trauma The organisms are saprophytic in nature and no doubt live in the soil on decaying vegetation especially on old logs from which they have been isolated

The disease is prevalent both in the temperate zone and in the tropics Cases have been reported from the United States Puerto Rico Cuba San Domingo Guatemala Costa Rica Brazil Argentina Uruguay Paraguay Venezuela Russia Japan Rhodesia Algeria Java and Sumatra

PATHOLOGY

Microscopically the lesion simulates tuberculosis or blastomycosis except for the fungi The epidermis shows a marked hyperkeratosis acanthosis and partial parakeratosis The corium exhibits intense infiltration edema and fibrosis associated with discrete granulomatous lesions These show central necrosis with areas of polymorphonuclear leukocytes in various stages of degeneration numerous lymphocytes plasma cells eosinophiles Russell s fuchsin bodies epithelioid cells macrophages fibroblastic changes discrete micro abscesses and giant cells of the Langhans or foreign body type arranged in tubercle like fashion Within the giant cells or in the abscesses the brown sclerotic cells of the fungus can easily be seen either as single cells or grouped in clusters

SYMPTOMATOLOGY

Chromomycosis is primarily cutaneous in origin Cases of systemic involvement have not been reported except in two isolated instances in which the lymph glands were involved There is very little pain or pruritus

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ETIOLOGY

To date two distinct strains of *Histoplasma* have been isolated in addition to several similar strains The first of these is *H capsulatum*, isolated and de-

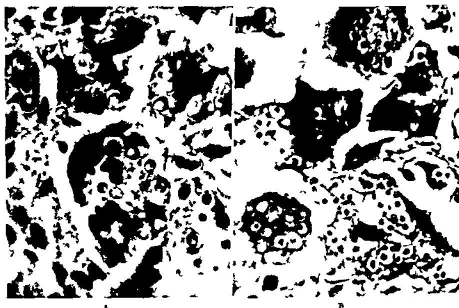


FIG 101 A Large cells of *Histoplasma* in tissue B Cells of *Histoplasma capsulatum* in tissue

scribed by DeMonbreun The second strain differs in certain morphologic respects as described by Moore The latter strain was isolated by Hansmann and Schenken from a forty three year old white male who had had a refactory skin ailment for sixteen years The organism was isolated from hard nodules on a scaly inflamed thickened skin and from the lymph node It now bears the name *H pyriforme*

In tissue *Histoplasma* appears as a simple or budding round or oval yeastlike cell approximately 1 to 4 microns in long axis usually 3 microns It is surrounded by a clear refractile and non staining capsule which equals approximately one sixth the total diameter It has a non homogeneous granular cytoplasm which may be vacuolated the nuclear material is usually eccentrically located near one pole The parasites are found chiefly in endothelial phagocytes but they may be found freely distributed in the affected area *H pyriforme* shows in addition to these small cells certain larger spherical cells measuring up to 5 or 6 microns in diameter some are larger (Fig 101)

In culture *Histoplasma* shows septate hyphae 1 to 5 microns in diameter sometimes with racquet mycelium Chlamydospores are found singly or in chains intercalary or lateral sessile or pedicellate they measure 3 to 10 microns in diameter Rarely terminal ones measure 3 to 10 by 6 to 20 microns Conidia are lateral spherical or pyriform and measure [illegible] to 8 microns in diameter Large tuberculate cells are at first spherical or clavate and measure

5 to 18 microns in diameter they are smooth and thick walled at first later becoming pitted then spinose and finally tuberculate The tubercles vary in form often resembling germ tubes but are functionless *H pyriforme* shows many pyriform tuberculate cells they measure 6 to 12 by 12 to °6 microns usually 10 by 2 microns

EPIDEMIOLOGY AND GEOGRAPHICAL DISTRIBUTION

Histoplasmosis as far as is known is not an epidemic disease The organism may be a saprophyte in nature but this has not been proved DeMonbreun reported a spontaneous infection in a dog

To date cases have been reported from the Canal Zone the Philippines Honduras Java Argentina Brazil and various states of the United States

PATHOLOGY

The gross pathology varies according to the clinical features of the disease In general however there are seen areas of necrosis superficial or deep Gray or white nodules representing pseudotubercles are seen in both the small and large intestines simulating miliary tuberculosis The liver becomes atrophied and cirrhotic Abscess cavities may occur in the lungs The peribronchial lymph nodes are enlarged and contain ulcerated tubercles The pleurae show fibrous adhesions or a fibrinopurulent process In the adrenals caseation is frequently encountered

Microscopically the necrotic areas show a central proliferation with loss of cellular structure and tissue There is a great deal of necrotic debris with a granulomatous response Fibrous tissue small foci of necrosis and large numbers of macrophages containing organisms are found distributed through this tissue response There are also giant cells of the Langhans or foreign body type polymorphonuclear leukocytes lymphocytes plasma cells eosinophiles and an increased number of capillaries Many of the phagocytes or histiocytes are endothelial in origin

SYMPTOMATOLOGY

Histoplasmosis presents a number of clinical features chief among which are emaciation severe anemia marked leukopenia splenomegaly enlargement of the liver and irregular pyrexia In some cases the hepatomegaly may be lacking while in others there may be no anemia splenomegaly or leukopenia There may be a systemic febrile condition similar to that of kala azar with a septic temperature curve Enlarged lymph nodes may simulate Hodgkin s disease lymphosarcoma or leukemia Ulcerated skin lesions have been noted in at least two cases that of Hansmann and Schenken and an unreported case of Moore and Blache The disease may be superimposed on tuberculosis of the lungs

DIAGNOSIS

In any case presenting any of these clinical features a diagnosis of histoplasmosis should be entertained Meleney advises the use of the many tests em

ployed in kala azar Van Pernis Benson and Holinger used broth filtrate and acetone precipitated substance from broth filtrate in 0 9 saline to obtain positive cutaneous reactions In any case the finding of the organism is the *only conclusive proof of diagnosis This may be accomplished by examination* and cultivation of sputum or blood by culture of material from the spleen liver lymph nodes or sternal puncture or by biopsy examination

PROGNOSIS AND TREATMENT

Prognosis is usually bad since diagnosis is not made as a rule until shortly before death The treatment employed has been varied Iodides have been of as little value as roentgen ray therapy has been Chemotherapy has been of some benefit where a pentavalent organic antimony preparation has been used *Local antiseptic treatment is of little value when the disease is generalized* Antimony preparations such as antimony tartrate fuadin (trivalent organic compound) and the pentavalent compound such as neostam may be helpful Surgery if not too extensive may have some value

ASPERGILLOSIS AND MUCORMYCOSIS

Certain members of the Aspergillaceae such as *Aspergillus Scopulariopsis* and *Sterigmatocystis* (*Aspergillus*) and others of the Mucoraceae such as *Mucor Absidia* and *Rhizopus* known as the weeds of mycology play an important part as contaminants of various lesions They are found in the soil and on dead or decaying organic material such as vegetables and fruit and can be isolated from numerous infections chiefly as secondary invaders

As agents of infection in man they produce disease which is chronic inflammatory and granulomatous in nature The organisms show a predilection for the pulmonary system They also involve the external auditory canal mucous membranes of the conjunctivae the cornea sinuses and occasionally the skin and the nails Since they can be found in dirty secondarily infected crusted cutaneous lesions their pathogenicity in these conditions should always be viewed critically Several of the genera however have been directly responsible for lung lesions and for mycetoma

HISTORICAL NOTE

The first description of aspergillosis in human beings is attributed to Bennet in 1843 Virchow in 1856 described the organism and reported the disease in the lungs and the external auditory canal The earliest scientific discussion of mucormycosis may be attributed to Furbringer who described two cases both with infections of the lungs Lang and Grubauer and Renon have reviewed the early literature adequately and have made valuable contributions of their own

ETIOLOGY

The common species of *Aspergillus* causing disease are *A fumigatus A flavescens* and *A niger* of the Mucors *Mucor mucedo Absidia corymbifera*

and *Rhizopus nigricans* may be pathogenic *Scopulariopsis brevicaule* and *Sterigmatocystis cinnamomeus* in addition to other species can cause disease

The fungi in tissue show at times the same characteristics that feature the

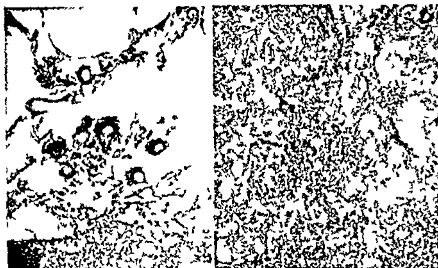


Fig 102 (A) Conidiophores of *Aspergillus* in lung tissue B Nodule of *Mucormycosis* in lung tissue

organism in culture exhibiting filaments spore heads spores and round cells

Culturally the Aspergillaceae and Mucoraceae show many types of colonies and colors In general the former grow rapidly producing somewhat flat to raised growths with a granular surface Microscopically they consist of specialized spore bearers termed conidiophores with phialides all borne on a stalk The hyphae are branched and septate The Mucoraceae show on culture rapidly growing colonies which are greatly raised above the surface of the substratum felted with long spore stalks at the apex of which is a spore sac the sporangium the whole being a sporangiophore Some species show rhizoids or rootlets at the base of the sporangiophore The hyphae are coenocytic branched forming hyphal bodies and chlamydospores

EPIDEMIOLOGY AND GEOGRAPHICAL DISTRIBUTION

The diseases are usually spontaneous and widespread throughout the world

PATHOLOGY

Pulmonary involvement (Fig 102) resembles tuberculosis closely The lesions are inflammatory with tubercle like formations The disease is either *parenchymatous* or *interstitial* The former shows congestion with or without ulceration of the mucous membranes of the bronchi and membranous patches The lesions

may be localized or generalized with the formation of tubercles and abscesses. The pleural surface becomes infected resulting in inflammation thickening fibrosis and pleuritic pain The interstitial type involves the alveoli Thrombi may be produced as well as atheromatous patches

Cutaneous lesions are either gummatous eczematous with verrucous formations mycetomas lymphangitis and ulcerations

Microscopically the cellular infiltrate is similar to that of other granulomatous lesions Surrounding and interspersed among the fungi there are leukocytes lymphocytes and giant cells the whole being more or less encapsulated by fibrous material and associated or not with central necrosis

SYMPTOMATOLOGY

Pulmonary lesions resemble bronchopneumonia or tuberculosis The acute type may exhibit marked toxemia The chronic type results in loss of weight night sweats cough asthenia anorexia and slight rise in temperature in the evening The cough becomes productive the sputum is streaked with blood and contains many organisms

Otomycosis is insidious in its onset with one or both ears mildly or extensively involved There may or may not be pain either sharp or acute in its early stages but in the later stages there is a feeling of puffiness The external canal and the tympanic membrane show accumulations of material which on examination consist of fungous elements

DIAGNOSIS

Diagnosis is best accomplished by isolating the causative agents and determining their pathogenicity

TREATMENT

Iodides may be helpful in early lesions of the lungs Cutaneous lesions usually disappear on treatment with antiparasitic drugs Rest and general hygiene are important

HEMISPOROSIS

This is an infection with a species of *Hemispora* (*H stellata H rugosa* or *H coremiformis*) These organisms produce in culture characteristic spores known as hemispores In tissue the organism is a yeastlike cell Clinically the disease manifests itself in lesions similar to those of sporotrichosis These consist of brass red nodules with varied irregular borders They are infiltrated pruritic papuloverrucoid and some are suppurative Mucous membrane involvement may also be noted Iodides are helpful as well as tartar emetic intravenously and antiseptics locally

CEPHALOSPORIOSIS

This is caused by members of the genus *Cephalosporium* which are similar to *Aspergillus* or *Penicillium* in the mode of spore formation but yet bear

some resemblance to *Sporotrichum* The organism has been isolated from ulcers dermatitis and gingivitis which were nodular or gummatous in appearance Like sporotrichosis the lesions succumb to iodides

ACLADIOSIS

This is caused by the genus *Acladium* with the single species *A castellanii* It is found in Ceylon the Malay States and Macedonia The lesions occur on the palms of the hands and soles of the feet At first they are small and commonly diagnosed as syphilis They are sharply defined ulcers roundish or oval with a red granulating fundus The purulent exudate forms crusts which are thick and yellow Gummatous nodules and furuncular lesions may also be found The organism is seen in culture as an unbranched growth with erect conidiophores and unicellular hyaline lateral sessile conidia Lesions do not heal spontaneously but are responsive to iodides

There are a number of other spontaneous isolated types of infection caused by single species but these are too numerous for consideration here

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SECTION NINE

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CHAPTER LVIII

INTRODUCTION

J ALLEN SCOTT AND Z T BERCOVITZ

THIS SECTION ON HELMINTHOLOGY HAS BEEN PREPARED with the requirements of the practicing physician especially in view Enough helminthologic detail has been included to enable him to understand the host parasite relationship and so to deal more satisfactorily with the problems of diagnosis treatment and prevention of helminth diseases It is expected that those interested will refer to the several available textbooks on helminthology in order to obtain details which cannot be included in this discussion Only those species of parasites which commonly infect man have been included There are several rare and unusual helminths which are occasionally found in human beings and for detailed lists and descriptions of such parasites the reader is referred to Faust s Helminthology

Evidence of intestinal helminthic infection such as the finding of ova or parasites in the stools does not necessarily indicate a clinical disease entity In fact many individuals frequently harbor several species of intestinal helminths without showing any clinical signs or symptoms that can be directly attributed to the parasitic infection In many instances the diagnosis is made in the laboratory as part of a routine examination

Helminthic infections are widespread throughout the world but are limited to various areas or population groups mainly by two factors namely the requirements of the life cycle of the parasites and the habits of the people Climatic and geographical conditions largely govern the continued existence of the different parasites by affecting the extra human stages of development Frequently the infections are chronic and affect large population groups As a result of these conditions problems of prevention and eradication of the infections must depend on governmental agencies

Since dietary and living customs are so frequently involved in the problems of control any attempt to control diseases of helminthic origin must include educational measures designed to change the customs which are at fault

The helminths are divided into two main groups *Platyhelminthes* and *Nemathelminthes* The *Platyhelminthes* are further subdivided into *trematodes* and *cestodes* The helminthologic aspects are discussed in the following chapters under the headings of trematode cestode and nematode infections Clinical laboratory diagnostic methods and treatment of helminthic infections are dealt with in separate chapters

eggs they are provided with an operculum or trap-door opening through which the larva eventually emerges When passed they are undeveloped and their only prominent internal features are a number of yolk cells They are readily distinguished from the eggs of all other human parasites except *Fasciola hepatica* which is occasionally found in man Barlow (19 5) states that the germinal area that is the protoplasm from which the larva will grow is clearly seen in the eggs of *Fasciola* but only with difficulty in those of *Fasciolopsis* and that in the former the number of yolk cells is usually fewer than the twelve to twenty seen in a single focal plane in the egg of *Fasciolopsis*

LIFE CYCLE AND METHOD OF TRANSMISSION

The eggs develop only in water at a temperature of nearly 80 F or above and the miracidia emerge in about three weeks or more These larvae are actively attracted to certain species of snails which are common in the water of the endemic areas and they are able to penetrate into their tissues in a few minutes time There the larvae develop into sacculate organisms known as sporocysts within which there develop a small number of mother rediae These emerge into the tissues and soon give birth to several daughter rediae which in turn produce large numbers of cercariae These larvae begin to leave the snail about four to six weeks after the miracidium has entered and although they can swim actively they usually make contact very soon with the plant on which the snail is feeding At once they attach themselves lose their tails secrete cyst walls about themselves and become metacercariae If they are attached to one of the various types of water nuts or bulbs commonly eaten while still moist the extremely friable outer cyst is usually broken by the teeth when the nut is peeled The larva then lies on the tongue covered with an inner cyst wall which is flexible and tough and protects it from mechanical and chemical damage until it has passed the stomach Upon reaching the intestine the cyst wall is digested away and the larva starts its development into an adult fluke reaching the egg laying stage about a month later

PATHOLOGY AND SYMPTOMATOLOGY

Experimental infections (Barlow 1925 Vogel 1936) show that symptoms begin one or two months after the cysts are swallowed and start with epigastric pains before meals Severe hypogastric pains that supervene are followed by diarrhea that is often severe and frequent but is not dysenteric and tends to alternate with constipation In massive infections edema appears early and involves the face limbs and abdomen but not the chest Ascites is one of the most common symptoms and anasarca develops in the later stages Untreated cases with large numbers of worms are often fatal death apparently being due to a general toxemia The local lesions at the point of attachment of the worms are generally of a minor nature although there may be some hemorrhage and secondary infections may produce ulceration The patients have an anemic appearance due to the edema but there is no reduction in red blood count or hemoglobin High eosinophilia is characteristic

CHAPTER LIX

THE TREMATODES OR FLUKES

J ALLEN SCOTT AND Z T BERCOVITZ

WITH ONE EXCEPTION THE FLUKES THAT CAUSE HUMAN disease are flat leaflike worms that have the reproductive organs of both sexes in the same individual When the eggs are hatched a ciliated larva called a miracidium is released This enters a snail either actively by penetration or passively by ingestion The development cycle within the snail results in the development of a second type of larvae which leave the snail and become free swimming and are known as cercariae If these larvae succeed in entering the human body they develop into the original type of adult worm Some species enter by actively penetrating the skin and some by being swallowed after they have encysted on or in human food plants or animals Therefore the etiologic and epidemiologic pictures associated with the different fluke diseases are extremely diverse even though the alternation of generations is characteristic of them all making necessary the successive infection first of man then of the snail and finally of man again

FASCIOLOPSIS BUSKI

The largest intestinal fluke of man *Fasciolopsis buski* (Plate XIX fig 4) is endemic only in the Orient and is most common in an area around Shaohsing Chekiang Province China where it infects a large proportion of the million or more inhabitants These flukes vary in size according to their age but tend to be smaller in poorly nourished individuals and in those who harbor large numbers of worms (Barlow 19 5) When fully grown they generally average about 30 by 12 mm but they may reach a length of 75 mm On account of their size they are not easily confused with any other flukes commonly found in the human intestine In experimental animals they are blood red or darker in color but may be considerably paler when passed in the stools They live attached to the wall of the small intestine into which they bury their spiny anterior end

The eggs are generally ovoid and average 138 by 83 microns in size but they frequently vary greatly in size and shape They are a yellowish brown in color varying in shade with different stool characteristics Like most fluke

Here thev develop into sporocysts in which rediae develop which in turn pro duce the cercariae These larvae attach themselves to certain species of fish especially the mullet in the case of Heterophyes (Khalil 1933) They then pen etrate the muscles of the fish and continue to develop for some time If the fish are eaten by certain mammals or are eaten raw by man the cysts are dissolved in the intestine and the young flukes begin to develop there

PATHOLOGY AND SYMPTOMATOLOGY

H heterophyes and *M yokogawai* apparently produce no symptoms in most persons but when present in large numbers they apparently cause gastric dis tress and diarrhea Related species in the Philippine Islands have been shown to bury deeply into the intestinal wall so that eggs can pass into the lymphatics and general circulation This is the interpretation which Africa *et al* (1935) place on their finding of worms deep in the intestinal mucosa and of eggs in the myocardium In the heart they found evidence of sudden embolism caused by large numbers of the eggs resulting in marked congestion edema and frag mentation of the cardiac fibers They found this picture in a number of cases of fatal heart failures and believe it to be the cause of many instances of heart failure attributed to beriberi and other diseases

DIAGNOSIS

The eggs of these flukes are very small and may easily be overlooked They are of a characteristic light chocolate brown color which makes them easy to recognize if one is accustomed to look for them The differentiation of these small fluke eggs is included in the discussion of the eggs of *Clonorchis* and *Opisthorchis* (page 754)

TREATMENT

No extensive studies have been made on the treatment of these flukes but they are known to be easy to dislodge Any of the common anthelmintics ap pear to be satisfactory for this purpose

EPIDEMIOLOGY

In Egypt *Heterophyes heterophyes* is a common parasite that is acquired by the eating of raw mullet The fish are pickled in salt and are eaten a few days later without being cooked The cysts will survive a week or more of salt ing In the Far East *M yokogawai* and other heterophoid flukes are trans mitted under similar conditions

PROPHYLAXIS

Personal prophylaxis consists in avoiding undercooked fish in the countries of the Near and Far East Control is difficult since animals other than man establish a reservoir of infection for which the fish constitute an important source of food The fish are found together with the snails in large bodies of water Education with regard to the danger of uncooked fish would seem to be the chief hope of eradicating these flukes

DIAGNOSIS

The characteristic eggs are laid in such numbers that positive diagnosis of a single worm can be made by examination of a smear from the stool Egg counts will tell whether the infection is heavy or light 900 eggs per gm of stool being roughly the number laid by the average fluke (Stoll Cort and Kwei 1927 Vogel 1936)

TREATMENT

Carbon tetrachloride has been used successfully in removing these worms but the toxicity of this drug should be kept in mind Caprokol crystoids were used by McCoy and Chu (1937) with fair results No reports have been seen of the use of tetrachlorethylene which might be useful for this purpose

EPIDEMIOLOGY

In the endemic area several types of plants with edible nuts or bulbs are grown in water as farm crops Freshly collected human feces aid in fertilization and the snail hosts which feed on these plants are everywhere abundant During the season the nuts are eaten fresh and are kept moist until sold when they are usually peeled with the teeth All elements necessary to maintain the epidemiologic cycle are thus present Elsewhere the infection is not so common for the cysts are often killed when the nuts are dried for shipment

PROPHYLAXIS

Personal prophylaxis consists in avoiding the fresh nuts Control of the infection seems possible Storage of night soil for three to five weeks or the introduction of lime kills the eggs Unfortunately the poorer farmers are not able to provide the necessary storage space Barlow has advocated mass treatment of the people and the use of lime on the fields to kill the snails

HETEROPHYES HETEROPHYES METAGONIMUS YOKOGAWAI

A number of small intestinal flukes parasitize man as well as the wild and domestic fish eating mammals in the Near and Far East *Heterophyes heterophyes* and *Metagonimus yokogawai* are the most common of these in man and are typical of the group They are small flukes usually less than 2 mm in length and inhabit the small intestine where they lie free in the lumen or between the villi They may sometimes penetrate into the wall in which case the eggs may enter the lymphatics Normally the eggs which are passed in the feces are very small not over 30 by 17 microns they are operculate and contain developed miracidia They are not easily differentiated from the eggs of related species and only by careful observation can they be distinguished from those of *Opisthorchis* and *Clonorchis*

LIFE CYCLE AND METHOD OF TRANSMISSION

When the eggs of these flukes fall in water they do not hatch but depend on being swallowed by the snails which act as the intermediate hosts They hatch in the stomach of the snail and then penetrate the tissues of the liver

massive long standing infections there is extensive destruction of liver tissue producing marked cirrhosis and obstructing the portal circulation

The symptomatology found in a series of patients studied in Korea by Bercovitz (1931) included indigestion epigastric distress swelling of the liver with or without ascites night blindness and leukocytosis with eosinophilia The indigestion and epigastric distress were usually responsible for the patient coming to the clinic but on physical examination marked enlargement of liver was the most prominent finding together with the leukocytosis and eosinophilia Fever was most noticeable by its absence The leukocyte counts ranged from 7 000 or 8 000 per cmm to as high as 30 000 a number of patients having from 19 000 to 23 000 leukocytes per cmm The eosinophiles ranged as high as 48 per cent It was noticed that when a secondary infection was superimposed upon the previous condition the eosinophilic reaction changed and the differential blood picture assumed that of the secondary infection

The enlargement of the liver was usually marked In some instances the liver extended to the brim of the pelvis and completely filled the already distended abdomen The liver was usually soft smooth with rounded edges and not tender The most noticeable finding was the prompt reduction in size as the result of biliary drainage with the duodenal tube The symptom of night blindness usually improved promptly with the reduction in size of the liver resulting from bile drainage

DIAGNOSIS

The characteristic eggs may be found either in the feces or in bile obtained through drainage with the duodenal tube In patients who have lived in an endemic area and who show the symptoms of indigestion and enlarged liver biliary drainage should be done for diagnosis especially if fecal examination is negative for ova of *Clonorchis* In the study of Korean patients it was observed that the ova could be found more readily following a dose of magnesium sulphate sufficient to produce a watery stool As a rule the second watery evacuation contained the ova when the first was negative In many instances stool examinations were negative even after Epsom salts and by concentration methods although the bile contained many eggs

TREATMENT

The various antimony preparations that are used for the treatment of schistosomiasis have been moderately successful in reducing the symptoms of clonorchiasis Emetine has also been used Gentian violet by mouth as recommended in the section on treatment of intestinal helminths (page 847) seems to be the most promising drug It may be given intravenously as in refractory cases of strongyloides It should be remembered however that in clonorchiasis there is extensive liver damage and any intravenous medications with gentian violet or injections of any of the antimony preparations should be made with great caution Patients should be hospitalized and given adequate therapy with glucose to protect the liver

THE HUMAN LIVER FLUKES

Two species of flukes commonly parasitize the human liver *Clonorchis sinensis* is the most common and most important but it is confined to the extreme Far East *Opisthorchis felineus* is only rarely found throughout the Far East but is common in certain areas of central Europe Both parasites are found in wild and domestic fish eating mammals as well as in man *Clonorchis* adults vary in length from 10 to 25 mm and in breadth they are generally about one half the length *Opisthorchis* is much narrower in proportion to the length which is usually from 7 to 12 mm Both worms inhabit either the bile passages of the liver or the crypts leading to them The eggs pass out with the bile and are found in the feces These eggs are operculate and more or less the same size as the eggs of *Heterophyes* and the other small intestinal flukes from which they are not always easily differentiated (Plate XIX fig 3) The eggs of *Opisthorchis* tend to be about three times as long as broad (approximately 30 by 11 microns) while those of the other species are roughly half as wide as long Those of *Clonorchis* and *Opisthorchis* contain well-developed *miracidia which have asymmetrically placed* organs while those of the intestinal flukes have bilaterally symmetrical organs

LIFE CYCLE AND METHOD OF TRANSMISSION

The eggs of these liver flukes do not hatch until swallowed by the snail host whereupon the miracidia penetrate the wall of the snail s digestive tract *and mature in the tissues into sporocysts (Hsu and Chow 1939* Vogel 1934) These produce a generation of rediae which in turn produce the cercariae The cercariae attach themselves to fresh water fish of the family Cyprinidae They penetrate the muscles of these fish and then encyst There is considerable growth and metamorphosis in the encysted stage Since in the endemic regions such fish are eaten partially cooked or only pickled these cysts are frequently intro*duced while still viable into the human intestine Here the* wall is dissolved and the young fluke emerging from the cyst ascends the bile ducts into the liver

PATHOLOGY AND SYMPTOMATOLOGY

The pathology of infections with these human liver flukes is proportional to the number of flukes present to the length of time the infection has persisted and to the constancy of reinfection Although these worms may live for many years most cases have few worms and show no noticeable symptoms and the serious cases seem to be the result of continual reinfection The early stages of the reaction and in fact the only reaction in most cases in which infection is light consists of hypertrophy of the walls of the biliary passages with additional thickening due to proliferation of the surrounding connective tissue This reaction may not be confined to the region immediately around the worm but apparently is stimulated elsewhere by a toxin secreted by the worm (Faust and Khaw 1927) In cases with a large number of worms the proliferation becomes sufficient to cause degeneration of the adjacent liver parenchyma and in

then appear in the sputum Some are swallowed and can be found in the feces The eggs average about 100 by 50 microns in size are operculate and of a golden yellow color (Plate XIX fig 2)

LIFE CYCLE AND METHOD OF TRANSMISSION TO MAN

The eggs in the feces or sputum are undeveloped but when they fall into water the miracidium develops and emerges within a few weeks It seeks certain species of snails into which it penetrates It then develops into a sporocyst which in about a month produces about twelve rediae Each redia produces about twelve more rediae and these in turn produce large numbers of cercariae which appear about ten weeks after the miracidium entered These cercariae penetrate into the muscles of crabs or crayfish where they encyst and go through a period of development before they are infective If these animals are eaten raw or undercooked the cysts are digested and the larvae emerge in the intestine The young flukes then penetrate through the intestinal wall into the abdominal cavity From there they may go to any organ but they tend to pass forward between the liver and the abdominal wall penetrating the diaphragm into the pleural cavity When mature they penetrate into the lungs Some go directly to the thorax and arrive in a few days while others may wander about for weeks (Yokogawa 1919)

PATHOLOGY

The worms usually localize near the bronchioles and become surrounded by a fibrotic cyst which ruptures into the bronchioles and afterward remains open The bronchi contain rather thick mucus in which there are disintegrating epithelial cells and occasional leukocytes The epithelial coat of the bronchus is often very much wrinkled and folded suggesting that there has been hyperplasia of the epithelial lining This is observed even in the bronchi which have well defined cartilaginous rings About the smaller bronchi one often sees a very rich infiltration of round cells At times these cysts may be caseating resembling tubercles or they may suppurate The cysts are usually filled with eggs as well as with a brown fluid which is discharged with them and which stains the sputum

SYMPTOMATOLOGY

In a clinical study of *P westermani* infection in an endemic area in Korea in which the infection rate was very heavy Bercovitz pointed out that cough and sputum were present in all cases and that bloody sputum was present in 95 per cent of the cases studied Fever night sweats shortness of breath and distress in the chest were found in 45 per cent while the symptoms of chills loss of weight loss of appetite and indigestion were present in 25 per cent or less of the patients Patients rarely become seriously ill and as a rule their ability to work is not impaired

At times the worms localize in tissues other than the lungs when the symp-

Biliary drainage with the duodenal tube was one of the most successful methods employed in the Korea series of patients (Bercovitz 1931) It was found that the flow of bile was easy to obtain and the reduction in size of the liver under biliary drainage was the outstanding feature of therapy It was found however that in spite of the rapid reduction in size of the liver ova of *Clonorchis* were found in the bile even though the patient was clinically improved and the stools negative The symptom of night blindness was promptly relieved by biliary drainage

EPIDEMIOLOGY

These parasites are found in animals in regions such as northern and central China where human infections are not common indicating that reservoir hosts are able to maintain the infection In areas of intense human endemicity however it has been observed not only that the eating of raw or insufficiently cooked fish is generally common but also that human feces often find their way into fish ponds from latrines built over the water (Faust and Khaw 1927) Since the cysts are not readily killed by salting pickling or drying the fish it seems likely that cases have arisen from imported fish in parts of the world where the infection is not endemic

PROPHYLAXIS

The avoidance of raw undercooked or pickled fish while in endemic regions makes possible perfect personal prophylaxis Control of the infection seems possible only through preventing the consumption of raw or partially cooked fish since reservoir hosts make eradication through sanitation impracticable In the worst endemic areas the serious infections might be considerably reduced by adequate disposal of human feces even though the infection were not eliminated

ENDEMIC HEMOPTYSIS—PARAGONIMIASIS—HUMAN LUNG FLUKE DISEASE

Flukes of the genus *Paragonimus* are commonly found in man in various parts of the Far East and are occasionally reported from other parts of the world including North and South America Similar flukes are present in minks and other mammals in the United States and elsewhere (La Rue and Ameel 1937) but it is not certain that these are a separate species Thus it cannot be determined whether the few human cases that occur outside the Orient are due to man s resistance to the variety ordinarily found in animals or to the fact that his food habits seldom expose him to the risk of infection

The worms are thick and rounded averaging about 10 by 5 by 4 mm They are normally located in the lungs but occasionally get into abnormal situations in other organs The lung tissue usually forms a cyst about the worms The eggs are laid in the cyst which eventually ruptures into the bronchioles They

PROPHYLAXIS

Personal prophylaxis consists in not eating raw or partially cooked crabs or crayfish The Japanese have made an attempt to control the disease by prohibiting the eating of raw crabs and claim to have achieved some success especially in larger towns where police power is most effective Attack on the snails is not feasible as they are operculate and can close up to exclude such poisons as may be applied Education probably offers the best hope of control of this disease

SCHISTOSOMIASIS BILHARZIASIS OR BLOOD FLUKE DISEASE

The three species of blood flukes which infect human beings are similar in life history and general mechanism of pathogenesis The syndromes produced by the different species are distinct however because of the different parts of the body in which the adults are located The three species also have different geographical distributions *Schistosoma haematobium* inhabits the veins of the bladder and nearby organs and produces the disease known as vesical schistosomiasis This species is common in many parts of Africa and only to a slight extent in adjacent parts of Europe and Asia The other two species inhabit the veins of the mesenteric plexus and produce slightly differing types of intestinal and hepatic schistosomiasis One of these *Schistosoma japonicum* is limited in its distribution to countries of the Far East while the other *Schistosoma mansoni* is found in various parts of Africa and in parts of South America and the West Indies The countries principally concerned in the latter region are Brazil Dutch Guiana Venezuela Puerto Rico and some of the Lesser Antilles Considering all species the two most important endemic areas are in Egypt and in the Yangtse Valley in China

Although the schistosomes are technically flukes or flatworms they are an exception to the rule in that their bodies are cylindrical and not flat Another peculiarity is that they are the only flukes in which the sexes are separate Although the three species vary somewhat in size and can be distinguished by microscopic examinations they all are superficially much alike The female is a slender threadlike worm usually about 15 to 20 mm in length and about 0 25 mm in diameter Along most of the ventral surface of the male there is a deep groove known as the gynecophoral canal within which the female spends most of her adult life Both sexes are provided with two suckers near the anterior end of the body with which they can attach themselves to the wall of the blood vessel The slender female is able to push farther into the narrow venules than the male and there she lays eggs as she withdraws

The eggs of the different human species of schistosomes are easily distinguished from those of other helminths They are all non-operculate and relatively large and contain fully developed miracidia (Plate XIX figs 5 6 7) Those of *S mansoni* have a large spine on the side which gives them such a characteristic appearance that even a broken shell can be recognized *S haematobium* has more slender eggs with a terminal spine which is usually

toms are related to the organs involved When the localization is in the brain the symptoms may simulate epilepsy paralysis of various types and cerebral hemorrhage When in the abdominal cavity the clinical impression may be that of generalized abdominal malignancy

DIAGNOSIS

The pulmonary infections with *Paragonimus* can almost always be diagnosed by microscopic examination of the fresh sputum It should be pointed out however that at times repeated examinations are necessary to discover the eggs especially if they are few in number and are found in individuals who have lived in an endemic area At times it is difficult to obtain from children because they swallow it In such cases the eggs are found in the stool These eggs have to be differentiated from the ova of the fish tapeworm The eggs are not present in tuberculosis sputum preparations

The roentgen ray diagnosis of *P westermani* is not satisfactory because there is no characteristic picture of the lungs in such cases Occasional dilatation of the bronchi has been noted Mottled shadows of various types have been associated with the disease but experience in Korea showed that those found were in patients with associated tuberculosis

TREATMENT

Various antimony preparations have been used for the treatment of paragonimiasis with indifferent success although symptoms often disappear following treatment Recently Yokogawa and others (1930) have had considerable success with injections of emetine hydrochloride and prontosil They gave intravenous injections of from 0 5 to 1 0 cc of a 4 per cent solution of emetine hydrochloride once or twice daily and intramuscular injections of 5 cc. of 2 5 per cent prontosil at the same intervals until the eggs showed a conspicuous degenerative change or had disappeared that is in from seven to seventeen days The symptoms were immediately improved the sputum was reduced in amount and became clear and several cases which were followed for several months showed no evidence of relapse Toxic manifestations including fatiguability anorexia abdominal pain nausea vomiting and diarrhea that were attributed to the effect of the emetine were present in some patients

EPIDEMIOLOGY

The custom of eating crabs or crayfish when raw salted or pickled seems to be the factor which determines the distribution of the disease in many regions There is a possibility that the worms of this genus commonly found in the muscles of the cat family in India belong to a different species from those commonly infecting man Since they are also found in dogs and other members of the Canidae in the pig rat and other animals it is probable that these reservoir hosts play important roles in the epidemiology of paragonimiasis in many regions

PARTIAL LIST OF PRINCIPAL SNAILS TRANS MITTING HUMAN TREMATODES

Sch stos ma haematobtum	
B l nus tr nc tus; Bul s dyb usk; Buli us c tortus	Egypt Cyrenaica and Tunis
B li us f sk l	Maurit us and pos bly Kenya Colony
Buli t op cus	South Af ica
Phys p is f ca	South Africa and th Belgian Congo
Phys psi globo a	S erra Leone West African Coast north ern N geria Nyasaland and Rhodes a
Phy op s nasuta	Kenya Colony
Pl norb s d fouri	Portugal and Morocco
Sch st som m s	
Pl norb bo yi	Egypt and Italian East Afr ca
Pl norb l ndri and Pl orb s h b ni	Sudan
Pl norb s pfe ff i	N tal Southern Rhodes a Sierra Leone
Plano bis sud nic	Nyasaland
Pl orbis ad uens	Belgian Congo
A t alorbis gl b t s (forme ly Pl b guad l u pen i other spec ecord d f th Western Hemisphere are synonym)	V nezu l Le Antilles Puerto R co Dutch Guiana nd Braz l
Sch t ma j p cum	
I t yam no oph a	Japan and the coast of Chin
K t yama fo mosa	Formosa
Oncomelani h pens i	Yangts Basin
Onc m l hyd b ps (Syn Bl f d quad)	Leyte Philipp ne Island
Cl no h nensi	
Par f rulus t tul; P fossarulus s ne i; B thyn fuch; B thy long or	Ch na and Japan
Op sthorch s f l neus	
B thyn a te tacul ta	
F ciol psi b sk	
Pl norb su; S gme t a ti d lla; S gme t na al th; S gm nt na s hmackeri; S gment hem phae l (S gm t na l g ll t); Gyraul s s g ne; H ppeut ntori	Ch na and Formosa
H t phy s h t phy	
P nell	
M t g mus y k i	
M l l b t a d other spe s of th g n	
Par g nimus u term	
M l a l bert na oth r species of the gen is A sime l t	

quite distinct while the egg of *S japonicum* is shorter and more rounded and has a minute sub terminal spine

LIFE CYCLE AND METHOD OF TRANSMISSION

The eggs are laid within the venules Since those of *S mansoni* and *S japonicum* are laid in the mesenteric branches of the portal system many are swept with the blood to the liver where they play no further part in the life history of the parasite although they contribute to the pathology Some of the eggs *however adhere to the capillary walls and are soon covered with a growth* of endothelial cells and are extruded from the blood vessel by a cellular reaction of its wall (Kohlschutter and Koppisch 1931) Many such eggs are permanently trapped in the tissues but those which are extruded from vessels of the bowel epithelium pass into the lumen and leave the body with the feces Likewise the eggs of *S haematobium* which are extruded from the vessels of the bladder wall pass in the urine but others are trapped in the tissues of nearby organs Relatively few eggs of this species reach the liver but some are carried to the heart and lungs A serious reaction in the heart and lungs is not common

When the eggs in the urine or feces fall into fresh water they hatch within a few hours and the emerging miracidia seek the snails which act as intermediate hosts *Penetrating into the snail tissues they develop into sporocysts* which produce a second generation of sporocysts which in turn produce the cercariae These larvae appear in the water about four to six weeks after the miracidium has penetrated the snail and may continue to emerge in swarms for weeks A single miracidium has been known to produce as many as 200 000 cercariae (Faust and Hoffman 1934)

The cercariae are attracted to human skin which they penetrate actively losing their tails On reaching a blood vessel they are carried to the heart and then to the lungs Because they are able to move through the capillaries they return to the heart and are carried into the general circulation from which they spread at random over the body Passing the capillary networks *they repeat this cycle until they arrive in the mesenteric arteries* whereupon they enter the portal system and locate in the liver Here they begin to feed and in the course of about six weeks become adult They mate and migrate in pairs against the portal current into the mesenteric plexus in the case of *S mansoni* and *S japonicum* or continue into the hemorrhoidal plexus in the case of *S haematobium*

PATHOLOGY AND SYMPTOMATOLOGY

A dermatitis is produced by the penetration of the cercariae into the skin The severity varies with the individual Some whose work keeps them in infected water experience no reaction whereas others may have reactions varying from isolated papules to a confluent involvement of large areas and sometimes urticaria Most persons experience intense itching for several days after infection and scratching often causes the lesions to become pustular (Barlow 1936)

are more abundant in the first morning specimen and in the last portion of each micturition The finding of eggs of *S japonicum* and *S mansoni* in the feces is more difficult but the methods described in the section on technique are useful Egg counts are useful in epidemiologic studies but in the individual case such counts show only whether many or few worms are likely to be present and they are probably less reliable in chronic cases Differential diagnosis of the intestinal conditions is relatively easy but the hepatic symptoms simulate those of amebic abscess other cirrhoses or similar conditions Serologic reactions are available but they are not of great value since they merely show that the infection is present and do not indicate whether it is contributing to the production of symptoms These techniques are time consuming and no more reliable than a search for eggs in the excreta Eosinophilia is an aid in distinguishing schistosomiasis from other conditions of non helminthic origin

TREATMENT

Fuadin a synthetic antimony compound has replaced tartar emetic nearly everywhere It is supplied in stable form in ampules can be injected intramuscularly without causing necrosis and produces less nausea vomiting coughing and cardiac distress than tartar emetic does Relatively few deaths have been reported as a result of this treatment (Khalil and Betache 1930 Khalil 1931 1933) Contraindications are advanced hepatic cirrhosis acute pyelitis cardiac diseases and pregnancy Patients should remain quiet for several hours after the injections Adults receive 1 5 cc of the 7 per cent solution on the first day 3 5 cc on the third day and then 5 cc on alternate days to make a total of about ten doses If eggs containing viable miracidia are passed a few weeks later five more injections can be given Surgical procedures to relieve advanced intestinal cases genito-urinary involvement or to remove greatly enlarged spleens have been used especially in Egypt

EPIDEMIOLOGY

The disease is confined to those regions in which certain species of snails are present and does not appear likely to spread much beyond its present limits Irrigation is usually responsible for the large numbers of snails which are instrumental in its endemicity but it can exist only where there is contact with and pollution of water containing these snails In Egypt at least seven million peasants are infected (Scott 1937) while in China the number must be many times as great In the latter country the wet cultivation of rice is an important epidemic factor (Faust and Meleney 1924) In Venezuela and probably other parts of the Western Hemisphere the infection is less widespread but where it does occur the prevalence and intensity are sometimes as high as in Egypt (Scott 1940 1942)

PROPHYLAXIS

Personal prophylaxis consists in avoiding all contact with untreated water unless it is known to be from a safe source Sand filters if well managed make water practically safe and storage for thirty six hours allows all the cercariae

Non human schistosomes also produce a dermatitis of a similar character which is usually more severe These larvae are not capable of producing infection in the human being for they are overwhelmed by the inflammatory reaction in the skin (Brackett 1930) Commonly known as water itch swimmer s itch and so forth this schistosome dermatitis has become an economic problem on commercially operated beaches in some regions (Cort 19 8 1936) It is common in some areas in the north central part of the United States as well as in parts of Canada and Europe Chemical treatment of snail infested water has been a fairly successful means of control (McMullen 1940)

The early symptoms of schistosomiasis are seldom recognized except in the case of persons who enter an endemic area and experience their first infection These symptoms are of a toxic character and the allergic reactions may differ with respect to the intensity of the first infection They include urticaria fever gastric disturbances respiratory difficulties generalized pains and are *accompanied by a leukocytosis with high eosinophilia* They may be easily confused with symptoms of malaria typhoid tuberculosis and other infections common in the tropics (Faust and Meleney 1924 Girges 1934 Pons and Hoffman 1933 Pons 1937)

In the case of *S mansoni* and *S japonicum* the most serious pathology results from the eggs which are carried into the liver When these are extruded from the blood vessels they are surrounded by an inflammatory reaction leading to the formation of pseudotubercles Continued passage of eggs into the liver produces severe hepatic cirrhosis which causes most of the fatalities from these two species (Faust and Meleney 1924 Jaffe 1937) Equally serious but less frequent is a pronounced splenomegaly while in both intestinal species the infiltration of eggs into the intestinal wall and the associated tissues leads to extensive fibrosis The development of papillomata abscesses and fistulae often follow Carcinomata and prolapse of the rectum are frequently seen in countries such as Egypt where many infected persons come under observation

The pathology of *S haematobium* is generally more local in type The bladder becomes hypertrophied and papillomata are often developed As the case becomes chronic the infiltration of eggs into the surrounding organs may cause fibrosis hyperplasia or even neoplastic growths in the tissues of the prostate testicles penis vagina or other organs Occlusion of the ureters and urethra is a common occurrence and secondary infection producing marked cystitis is to be expected in advanced cases The eggs of any species may lodge in the capillaries of the brain lungs myocardium and other organs producing symptoms difficult to differentiate from other reactions in these organs

DIAGNOSIS

Diagnosis of the early stages of dermatitis and toxemia is difficult and can be made only on the basis of the history and by the elimination of other possibilities In the later stages the occurrence of eggs in the excreta is strongly presumptive but the need for differential diagnosis remains The eggs of *S haematobium* are readily found in the urine after sedimentation and preparations can be dried on a slide for later examination (Barlow 1931) The eggs

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to die They are also killed at temperatures considerably below boiling Control of the disease by snail reduction through clearance of vegetation from the canals has been started in Egypt (Barlow 1937) while a similar reduction through changes in irrigation construction and management seems possible in Venezuela (Scott 1942)

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nata) are ordinarily about o mm long and 14 mm broad and contain a uterus with more than fifteen compound branches on each side of the central stem Those of the pork tapeworm (*T solium*) on the other hand are seldom longer than 15 mm and are usually about 8 mm broad The uterus in this species never has more than thirteen branches on each side of the central stem The gravid proglottids as seen in the feces may be motile and therefore may be mistaken for flukes Those of *T solium* are characteristically passed singly and may be sufficiently active to pass the anal sphincter during the night Those of *T saginata* are more likely to be found in groups in the feces

The mature proglottids of both species are characterized by their rectangular shape They can be differentiated from each other only by a study of their detailed anatomy The male and female systems open into a common atrium which is connected by a single genital pore located in the middle of the lateral margin of the proglottid These openings alternate irregularly on the right and left sides of successive proglottids

The scolex of *T solium* is more or less spherical and about 1 mm in diameter It has four lateral suckers surmounted by a rostellum on which is a double row of about thirty hooks The scolex of *T saginata* which may be nearly twice as large has no rostellum or hooks Its four suckers are so shaped as to make the scolex appear approximately square

T solium ordinarily has nearly 1 000 proglottids and is about 2 meters long It is seldom more than 3 meters long or has more than 1 000 proglottids *T saginata* on the other hand characteristically has from 1 000 to 2 000 proglottids and since these are usually longer than those of the pork tapeworm (*T solium*) the entire worm is usually 4 or 5 meters long and may occasionally be very much longer

The eggs of these two species are indistinguishable from each other but can be distinguished from those of other human tapeworms They are usually between 35 and 40 microns in diameter and can be recognized as tapeworm eggs by the three pairs of hooklets embedded in the spherical hexacanth embryo (Plate XVIII) The shell or embryophore is composed of radially arranged truncated prisms and it is this radial structure which serves to differentiate the eggs from those of tapeworms belonging to other groups

LIFE CYCLE AND METHOD OF TRANSMISSION

The embryo freed from the egg shell in the bovine or porcine intestinal tract penetrates the intestinal wall migrates through the circulatory system and becomes embedded in the muscles Here it develops into a cysticercus This larva consists of an ovoid bladder into which is invaginated a scolex similar to that of the adult When recovered from the meat these larvae appear as nearly clear bladders about the size and shape of a pea or small bean and contain a white spot of pin head size If these reach the human intestinal tract in a viable state the bladder is digested the scolex evaginates and attaches itself to the intestinal wall Here it begins to proliferate proglottids which may be mature within six weeks time The larval stage of *T saginata* is known as

CHAPTER LX

THE CESTODES OR TAPEWORMS

J ALLEN SCOTT AND Z T BERCOVITZ

THE HUMAN TAPEWORMS ARE ALL SIMILAR AS FAR AS THE general structure of the adult worm is concerned but differ in respect to the morphology of the larval stages and in the methods by which they pass from one definitive host to another The adults are often considered degenerate organisms in that they have no digestive system but absorb nourishment through the integument directly from the milieu The head or scolex serves only to attach the worm to the intestinal wall and may bear organs of attachment such as hooks and suckers which are helpful characteristics in the differentiation of the species The posterior portion of the scolex has the power of proliferation and from it a series of segments or proglottids continues to be produced throughout the life of the worm Each proglottid is an individual in itself as far as reproduction is concerned although the simple nervous and excretory systems pass through the entire chain

In viewing the entire worm one finds at the anterior end immature proglottids in progressively more advanced stages of development Lower down are the proglottids with mature reproductive organs sometimes those with mature male systems being anterior to those with mature female systems Finally at the posterior end are the gravid segments containing eggs These segments are progressively sloughed off

THE BEEF AND PORK TAPEWORMS

The two species of human tapeworms (*Taenia saginata* and *Taenia solium*) acquired by eating beef or pork containing the viable larvae are closely related species They are clinically different in that the pork tapeworm (*T solium*) may occur in man not only as a relatively benign adult worm but in the larval stage as well This latter stage the cysticercus may produce a clinical state with a grave prognosis

Both worms are easily distinguished from other large human tapeworms by the fact that their gravid proglottids are longer than they are broad Moreover they are characterized by the presence of a uterus with a central stem and lateral branches The number of these branches is a useful means of distinguishing between the two species The gravid proglottids of the beef tapeworm (*T sagi*

in the stools are disintegrated a saline cathartic may cause recognizable ones to be passed or diagnosis can be made after the worm has been removed by treatment In any case specific diagnosis is important as a basis for interpretation of any later symptoms which might be cysticercosis should *T solium* be present

The diagnosis of cysticercosis is often difficult In the superficial tissues specific diagnosis usually follows excision Complement fixation tests (Culbertson 1941) have been successful in recognizing the presence of cysticercosis while in the vital organs roentgenograms may show the presence of calcified cysts (MacArthur 1933 and 1934) Otherwise diagnosis must depend on interpretation of the symptoms in which case a history of infection with the adult *T solium* is suggestive Eosinophilia may offer a clue if no other helminth infection is present Epilepsy in families without a history of such seizures and living in the endemic areas is suggestive of cysticercosis of the brain

TREATMENT

Oleoresin of aspidium is the drug most commonly used for the removal of adult tapeworms The method of administration and toxicity is discussed in the section on treatment of intestinal worms (page 846) Multiple doses of caprokol crystoids are less toxic and appear to be effective in some cases In any case the stools should be searched for the head since if the worm is broken after it has been loosened the head may be able to attach itself to the intestine in a new position and produce a new chain of proglottid

Treatment of cysticercosis involves excision if in an operable position otherwise only symptomatic treatment is possible No drug to kill the larvae is known and there is evidence that the dead and calcifying cysts in the central nervous system do more harm than living ones

EPIDEMIOLOGY

T saginata is found all over the world wherever beef is eaten The prevalence of *T solium* is generally proportional to the extent to which pork is eaten raw Infections with *T solium* are rare in the United States compared with *T saginata* As a rule the cysticerci are more common in the animals concerned than are the adults in man since the eggs are more effectively spread Human sanitary habits play an important part and improvements in this respect together with introduction of meat inspection have apparently reduced the prevalence of the infection in some countries

PROPHYLAXIS

The infection with adult worms can be avoided through eating no raw or rare beef or pork Feces of infected persons should be handled with the greatest care and prompt treatment given for *T solium* to obviate self infection Inspection of meat is a fairly effective preventive as the cysticerci are more common in some muscles that can be readily examined (Hall 19 8) Freezing at 15 F for six days kills the larvae Sanitation of feeding ranges of hogs and cattle in endemic areas should be of value

Cysticercus bovis and that of *T solium* is *Cysticercus cellulosae* They differ only in the structure of the head which in each case resembles that of the adult

PATHOLOGY AND SYMPTOMATOLOGY

The two species produce similar effects as far as the adult worm is concerned Most cases probably show no symptoms and are recognized only when the proglottids are found either in the stools or in the clothing Digestive disturbances with which pains may be associated are the most common symptoms (Swartzwelder 1939 Penfold 1937) There may be hunger pains increased appetite loss of weight and general weakness Anorexia extreme dyspepsia and diarrhea are mentioned in the literature but were not common in the large series of cases reported by Swartzwelder and Penfold Nervous complaints may be due to a toxin may be traced to the digestive disturbances or may be merely a psychological effect of the knowledge that proglottids are being passed A few cases have been reported of pseudo appendicitis or perforation of the intestine with peritonitis The infection may last for a great many years without doing any appreciable harm Eosinophilia is common but not invariably present

Cysticercosis Human infection with *Cysticercus bovis* is so rare that from a practical standpoint it need not be considered Infection with *Cysticercus cellulosae* is found occasionally in most parts of the world and is common in certain areas *Cysticercosis cellulosae* constitutes a grave danger for those who harbor the adults of *T solium* since infection with the larval form may arise from swallowing the eggs or from possible internal autoinfection The symptoms and pathology vary according to the organ and tissues involved A common site is the subcutaneous tissues where the reaction is usually local The larva always becomes encapsulated with fibrous connective tissue and in such favorable sites as the subcutaneous tissues it can be removed intact within the capsule *The most common site in which serious effects are produced* is the central nervous system Here again the effects vary with the site but symptoms resembling epilepsy are the commonest type of reaction (MacArthur 1933 Dixon and Smithers 1934) Other common sites are the muscles liver lungs and heart

DIAGNOSIS

The finding in the stools of eggs (Plate XVIII) with six hooklets and of shells with a radial structure indicates that one or the other of these species is present Usually cases are recognized when proglottids are found in the stools or on clothing From these gravid proglottids specific diagnosis can be established The proglottids should be washed in water pressed between glass slides and held to the light Sufficient detail can usually be seen without magnification For purposes of demonstration the uterus can be injected with India ink The lateral genital pore distinguishes the segment from the flukes and together with the size and elongate shape aids in distinguishing it from other species of tapeworm The differentiation between *T solium* and *T saginata* can be made on the basis of the number of uterine arms If all the proglottids

in the stools are disintegrated a saline cathartic may cause recognizable ones to be passed or diagnosis can be made after the worm has been removed by treatment In any case specific diagnosis is important as a basis for interpretation of any later symptoms which might be cysticercosis should *T solium* be present

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ECHINOCOCCUS GRANULOSUS

The hydatid cyst is the most serious of all human tapeworm infections These cysts are the larval stages of *Echinococcus granulosus* and perhaps other related species the adults of which are found in dogs and other carnivores but not in man Normally these larvae develop in sheep cattle or other animals and the human infection is accidental In areas where the infection is endemic in animals human infection is common elsewhere it is occasional

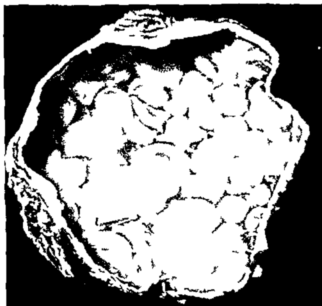
The adult worm is small rarely over 5 mm in length and usually has only three or four segments The eggs cannot be distinguished from other tapeworms of dogs and are like those of the human taenias The gravid proglottids which can be found most easily in the stools of a dog after he has been purged can be easily identified by their small size (• mm in length) and by the short lateral arms of the uterus

LIFE CYCLE AND METHOD OF TRANSMISSION

The embryo emerging from the egg in the intestine of the intermediate host penetrates the intestinal wall and is carried in the circulation to the liver or sometimes beyond this to other organs There it develops into a cyst or hydatid which is often of large size and within which a multiplication of daughter cysts brood capsules and scolices may develop If the cyst ruptures a metastasis may occur and each of the scolices may start the development of a new cyst in whatever tissues it may be localized Moreover some types of cysts are never encapsulated and metastases are of regular occurrence

Since the cysts in man do not become available to dogs the life cycle is not continued from human infection In the natural life cycle sheep cattle or pigs are ordinarily involved they become infected from the eggs in feces of dogs scattered on their pasture Dogs become infected by eating the offal of slaughter houses or an occasional dead animal on the range Human infection usually results from contamination of drinking water or by eggs that are passed by the hands to the mouth after handling dogs

The usual variety of hydatid cyst (Fig 103) in most areas is in the unilocular cyst Most of these are the result of infection acquired in childhood As the growth is slow no symptoms may be noted for many years unless the cyst is in a confined position where pressure produces unpleasant effects These unilocular cysts have a characteristic outer laminated and very elastic layer Outside of this the host forms a fibrous tissue capsule which is intimately connected with the surrounding normal tissues The cyst is filled with a clear hydatid fluid When the cyst has reached a size of about 1 cm after about five months the inner germinal layer begins to proliferate From it there grow stalked vesicles known as brood capsules which may later become detached and float free in the fluid The inner layer of these capsules invaginates and forms a number of scolices with suckers and hooks like the adult Eventually the fluid of the cyst may contain so many of these brood capsules and free scolices (Fig 104) that they form a deposit in the fluid known as hydatid sand



Fic 103 Hydatid cy t ith brood capsules (Courtesy of S H Polayes)



Fig 04 S ol ces from hyd t d cyst (Cou tesy of Dr Louis R Da dson)

Occasionally the adventitious fibrous tissue capsule may contain weak spots through which the two layers of the cyst proper may herniate (Dew 19 8) Portions of the cyst may become separated and develop into new cysts in this case known as exogenous daughter cysts

SYMPTOMATOLOGY

The clinical symptoms of hydatid disease are dependent on the size of the cyst and its location in the body About three quarters of the unilocular cysts of primary origin are found in the liver The lungs are the next most frequently attacked organs and any of the other organs of the body may occasionally be affected Small cysts as a rule cause no symptoms and are discovered only as part of routine roentgen ray examinations When the cysts become larger attention is directed to their presence and usually the diagnosis of a tumor of some type has to be considered Hydatid cysts of the liver are most frequently in the lower pole of the right lobe and when they become large are easily palpated As a rule no symptoms are noted except the fullness in the upper right abdomen Cysts invading the lungs (Fig 103) usually do not cause symptoms until their size causes pressure with resulting unproductive cough more or less shortness of breath and possibly pain in the chest Peritoneal cysts are relatively common but many of these are secondary Brain cysts occur and are of an especially serious nature The symptoms produced by brain cysts are dependent on their location and localization of the cyst requires the consultation services of a neurologist

If the cysts are invaded by secondary bacterial infections the prognosis usually becomes more grave Occasionally however these infections sterilize the cysts of scolices and then die out In some cysts scolices are never produced in which case they are known as sterile cysts or acephalocysts

When leakage of the hydatid fluid occurs eosinophilia may develop otherwise the increase in these cells is local Extensive leakage produces anaphylactic reactions which in the case of rupture are often extremely serious Emboli due to scolices from ruptured (cardiac) cysts have caused sudden death (Dew 1937 Khalil 1934) The usual pathologic effects of the infection are however those produced by the pressure of growing cysts on adjacent tissues In the head the effects rapidly lead to serious reactions In the bone extensive necrosis of the osseous tissue may result from the pressure In softer tissue such as the liver the infection may exist for many years and the cyst reach a large size before producing any noticeable effects

DIAGNOSIS

Hydatid disease should be considered in the differential diagnosis especially in endemic regions when a tumor is present the etiology of which cannot be determined This statement applies especially to conditions in the chest or liver which cannot be attributed to some other obvious pathologic condition The complement fixation reaction is the most reliable diagnostic method but the intradermal (Casoni) test and roentgen ray films are also useful aids

Thompson and Bercovitz studied a series of 43 patients with both the Casoni test and the complement fixation test Fifteen patients were found to have hydatid disease and in all but one of these the complement fixation test was



Fig 10 Hydatid cyst of the lu

positive Of the 28 patients who did not have hydatid disease all but one were negative to the complement fixation reaction There was only one false positive reaction On the other hand in the case of the intradermal (Casoni) test there were five false positives It appears that a negative Casoni test is reliable but the positive reactions must be considered in the light of other clinical findings

Nervous symptoms masses in the chest not attributable to tuberculosis liver tumors of obscure etiology and bone involvements simulating tuberculosis and other infections are all suggestive of hydatid disease Roentgen ray films

are useful for diagnosing hydatid especially in the bones and lung The cyst shows a characteristic sharp outline The most useful methods however are the various serologic tests Exploratory operations where removal would be impossible are not advised Under no conditions should aspiration be attempted except under surgical exposure of the cyst and then only under conditions which allow for injection of formaldehyde and removal of the cyst

TREATMENT

The only treatment for hydatid cyst is surgery In many sites the cyst can be removed intact but this is often difficult since the adventitious fibrous capsule around the cyst shades gradually into normal tissues so that enucleation is impossible Even in locations considered operable surgeons experienced in this field expect many recurrences from spilled scolices If the cyst cannot be removed intact the fluid is partially aspirated with the greatest care into closed containers Then 10 per cent formalin is introduced and the surrounding tissues swabbed with the same solution About ten minutes later the fluid can be completely withdrawn and the cavity obliterated This usually serves to kill the germinal tissues and to prevent further growth (Loucks 1930)

EPIDEMIOLOGY

With few exceptions hydatid infections are of world wide distribution Only in a few areas however do they appear more than occasionally In Iceland the former high endemicity has been reduced In the sheep and cattle raising regions of southern South America and in Australia and New Zealand the infection is highly endemic In New Zealand about 120 cases are treated each year of which 16 are fatal Half of the sheep and cattle are infected and one third of the country dogs harbor the adult worms In the Mediterranean region and in central and northern Europe the infection is common and it is highly endemic In Syria the infection rate in man is always lower than that in animals since it is for him an accidental infection In areas of low prevalence the occasional cases in man are perhaps more frequent than would be expected In North America less than 1 000 scattered cases have been reported (Magath 1937 Sawitz 1938) Dogs are rarely infected and the larval stages are most common in hogs Infection in moose and wild Canidae has raised the question as to whether the reservoir in this continent may be a wild rather than a domestic animal (Riley 1933)

PROPHYLAXIS

Care in avoiding drinking water and possibly vegetables which may have been contaminated by dogs in endemic areas is advised although it has not been proved that human infection arises in this way Handling of dogs or of sheep whose wool has been contaminated is apparently the usual means of infection in endemic areas and prophylaxis consists in not putting the fingers in the mouth and in careful washing of the hands before eating Control has apparently been effectively accomplished in some places by keeping dogs away

from slaughterhouses cooking all offal used as fertilizer and educating the people in the danger of children fondling dogs In other areas no progress has been made Turner Berberian and Dennis (1936) have shown that dogs may be immunized and suggest this as a means of control

HYMENOLEPIS SPP

Hymenolepis diminuta is a cosmopolitan parasite of rats and mice which occasionally infects man In many parts of the world rats and mice as well as man are commonly infected with the so called dwarf tapeworm These worms in the rodents have been named *Hymenolepis fraterna* while those in man are called *Hymenolepis nana* The two types are morphologically identical and since various rodent strains differ as much physiologically between themselves as they do from the human strain (Shorb 1933) the tendency is now to call them all *H nana* Those of rodents are often called *H nana* var *fraterna* to distinguish them from the human strain without implying a specific difference

All worms of this genus have proglottids broader than long *H diminuta* is usually about 20 to 70 cm in length if as is usually the case many worms are present in the infection Its width seldom exceeds 1 mm The scolex of *H nana* is equipped with four suckers and a hookless rostellum which can be invaginated into the anterior part of the head The gravid proglottids become completely filled with eggs obliterating any sign of the uterine shape They are not ordinarily seen in the feces however but whenever infection is present the eggs (Plate XVIII) can be readily found on microscopic examination of the feces The eggs of both species contain embryos with six hooklets and are surrounded by what are loosely spoken of as two shells The space between the shells is filled with a colorless gelatinous substance In the case of *H diminuta* this space is clear while in that of the viable eggs of *H nana* loosely twisted filaments can be seen Moreover the diameter of the eggs of *H nana* varies from 30 to 50 microns while those of *H diminuta* are larger measuring from 60 to 80 microns in diameter and the latter also tend to be more ovoid

LIFE CYCLE AND METHOD OF TRANSMISSION

The life cycle of *H diminuta* resembles that of other tapeworms in that the eggs swallowed by the intermediate hosts develop into cysticercoids The intermediate hosts may be any of a number of insects The rodents are infected by swallowing the insect infected with the cysticercoids It is thought that the occasional human cases may arise from swallowing infected meal beetles in precooked cereal

The life cycle of *H nana* is very unusual in that no intermediate host is required When the eggs are swallowed by man or rodents the embryo burrows into a villus and there develops into a cysticercoid larva When fully developed it emerges attaches itself to the intestinal wall and matures the eggs appear in from two to three weeks after infection (Woodland 1924) It has also been

shown that insects become infected with cysticercoids of this worm and that infection can be acquired by the definitive hosts if these infected insects are swallowed (Bacigalupo 1929) A third possibility is autoinfection the eggs hatching without leaving the host Hunninen (1936) has shown that in mice autoinfection is possible but probably not usual and as far as known a similar situation may exist in man and may be the explanation of occasional very heavy infections References to interesting studies on immunity to this infection are given by Hearin (1931)

PATHOLOGY AND SYMPTOMATOLOGY

Most persons especially those with few worms show no symptoms from this infection The symptomatology has not been adequately studied under controlled conditions where the possible effects of other parasites have been excluded Infections with hundreds of these worms are common and some with thousands are not at all rare The most common complaints are gastro intestinal including abdominal pain and diarrhea Various nervous symptoms including epileptiform seizures have been attributed to this infection and are thought to be due to a toxic effect No permanent pathologic damage has been demonstrated

TREATMENT

H nana is most common in young children and since they are most susceptible to the toxic effects of aspidium this drug is seldom recommended for this infection Carbon tetrachloride has been used effectively but that too is toxic Its non toxic relative tetrachlorethylene may be a good substitute but some success has been achieved with the use of multiple doses of the more easily administered caprokol crystoids given as described in the section on treatment of intestinal worms (page 84?)

EPIDEMIOLOGY

It is not certain how frequently human infection with H nana arises from rodent sources Experimental evidence so far is not conclusive but indicates that such infection is possible although not often very probable The epidemiologic evidence on the point is conflicting It seems certain that there is adequate opportunity for the occurrence of hand to mouth infection with eggs of human origin in most environments just as is the case with ascaris and trichuris (Chandler 1927 Brumpt 1933 Otto 1936) The similar distribution of all these worms emphasizes the point

Infection with *H nana* is most common in warm climates In the southern United States where it is most prevalent in young children its prevalence is greater in mountain regions than in the coastal plains In a few localities as many as 10 per cent of the children are probably infected but almost everywhere the prevalence is less than 1 per cent (Keller Leathers and Knox 1938) In the tropics the infection is often much more common

PROPHYLAXIS

Massive infections with these worms probably seldom exist in the presence of good personal hygiene No record of diminution of infection following control measures has been noted Provision of sanitary facilities designed to accommodate children in addition to educational measures should be of value If rodents prove to be an important factor in the epidemiology measures for rodent reduction should be useful

THE BROAD OR FISH TAPEWORM

This tapeworm has been called by several names including *Bothriocephalus* and *Dibothriocephalus* but it is now agreed that the correct scientific name is *Diphyllobothrium latum*

D latum is a very large worm usually 5 to 10 meters long and about 1 cm wide but specimens have been recorded which were very much longer Often as many as 3 000 proglottids may be present The head is elongated and bears two slit shaped suckers one on either side The mature proglottids are distinguished from those of the Taenias in that they are wider than long commonly about 3 by 10 mm The male and female systems open into a common genital pore on the midventral line and behind this is located the birth pore or uterine opening The gravid segments have a conspicuous rosette shaped uterus in the center The eggs are extruded from the birth pore at intervals The gravid proglottids are seldom found in the feces but the eggs can always be found in the feces of infected persons These eggs resemble those of the flukes more than they do those of other human tapeworms in that they are provided with an operculum (Plate XIX) They are of a yellow color and measure about 45 to 75 microns Little can be seen inside except a mass of yolk cells

LIFE CYCLE

The eggs may be passed in numbers as great as a million a day They are quite susceptible to drying and must fall into water before development can proceed In the water the embryo requires about two weeks to develop and then emerges from the egg shell as a coracidium a spherical ciliated larva in which six hooklets can be seen This larva lives for only a matter of hours unless it is swallowed by a water flea a crustacean such as Cyclops or some related genus In this host the larva localizes in the body cavity and in about three weeks it has developed into a procercoid This larva is an elongated form measuring about 0 5 mm and bears at one end a spherical appendage in which the six hooklets can be seen For the next stage in the life cycle the crustacean must be swallowed by fish Freed in the stomach of the fish the larva penetrates into the muscles where it becomes considerably more elongated reaching a length of 1 or 2 cm and a diameter of 2 or 3 mm At this stage the larva is known as a plerocercoid or sparganum It is not encapsulated by the host tissues but lies in a twisted knot between the muscle fibers If the infected

fish is eaten by the definitive host without sufficient cooking these larvae develop into adult worms Large fish may acquire the infection by eating smaller infected fish There is no growth in the second fish but the infection can be passed on to man

PATHOLOGY AND SYMPTOMATOLOGY

Birkeland (1932) made a careful review of the literature on the clinical effects of this infection In most cases there are no symptoms whatever In Finland especially but to a certain extent in other regions as well a small percentage of the infected people develop a profound anemia indistinguishable from pernicious anemia except that it is relieved by removal of the infection It seems apparent that there is some predisposing factor and that the worm merely precipitates the anemic state Syndromes are also recognized which are probably due to the same mechanism but have not progressed to the stage of anemia This effect has not been seen in autochthonous cases in the United States

Abdominal pain is most common among the other symptoms but various other digestive disturbances occur At times glossitis and stomatitis are the only symptoms Various neurotic states have also been described and reported to disappear after removal of the worms

TREATMENT

Aspidium which is recommended for other tapeworm infections is used to remove the broad tapeworm Carbon tetrachloride has been used but its toxicity should not be overlooked

Tetrachlorethylene and caprokol crystoids have not been extensively used for this infection but might be effective They do not involve the danger of toxic reactions

EPIDEMIOLOGY

The fish tapeworm is common only where the people are accustomed to eating uncooked fish although in these regions persons who eat only cooked fish may become infected if the cooking is not sufficiently thorough Drying salting smoking and pickling are frequently not thorough enough to kill the plerocercoids

The infection is most common on the shores of the Baltic but also occurs around some lake districts of central Europe It is also present in much of Eastern Europe in Palestine Siberia and the northern part of the Far East Migrations of Baltic inhabitants have brought the infection to North America where it has become endemic in the lake districts of the central United States and Canada In these latter regions the infection is maintained through the dietary customs of the people of Baltic descent The emptying of urban sewerage systems into streams and lakes is considered to be an important factor Wild animals have been found to be infected and may act as reservoir hosts making eradication difficult (Magath and Essex 1931)

PROPHYLAXIS

Personal prophylaxis consists in eating well cooked fish only while in the endemic regions Control should be at least partially effective if the water is adequately protected from human pollution while education with respect to eating habits is another possibility

SPARGANUM INFECTIONS

The plerocercoid or sparganum stage of various relatives of *D latum* has been found infecting the subcutaneous tissues and musculature of man In the United States the infection may be more common than realized (Mueller 1938 Mueller and Colston 1941) and is probably due to *S mansonoides* which normally infects mice In the Far East the infection is usually due to *S mansoni* and frequently occurs in the eye as a result of the use of freshly killed frogs for poultices The larvae of this species are normally found in frogs and migrate into the conjunctiva causing severe pain and considerable damage Ordinarily infection probably occurs through swallowing Cyclops infected with these organisms *S proliferum* is a species which grows and branches and buds off large numbers of spargana which invade the tissues and cause acne like lesions of the skin or in the case of deeper tissues cause death There are 6 cases of this form on record in Japan and one from Florida in the United States The adult is unknown nor is it known whether the proliferation is normal to this species or a reaction peculiar to an abnormal host Diagnosis of sparganosis can be made by dissecting out the organism It is important from the point of view of prognosis to differentiate the unbranched forms from the proliferating type Prophylaxis consists of drinking only boiled or filtered water in endemic areas and educational measures with regard to the use of poultices of freshly killed animals

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PLATE XVIII

Ova of Helminths

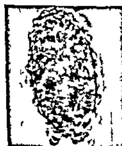
Ova of some of the human helminths and rhabditiform larvae of hookworm and strongyloides (See also Plate XIX)

1 *Ascaris lumbricoides* (unsegmented)
2 *Ascaris lumbricoides* (embryonated)
3 *Ascaris lumbricoides* (segmenting)
4 *Ascaris lumbricoides* (unfertilized)
5 *Ascaris lumbricoides* (decorticated)
6 Hookworm (segmenting)
7 Hookworm (morula)
8 Hookworm (embryonated)
9 Hookworm larva (rhabditiform)
10 *Strongyloides stercoralis* larva (rhabditiform)
11 *Trichuris trichiura*
12 *Enterobius vermicularis*
13 *Taenia* (note hooklets)
14 *Taenia* (note radial striations)
15 *Hymenolepis nana*

All photomicrographs × 450 Ascaris (segmenting embryonated unfertilized decorticated) hookworm larva (*Paragonimus Clonorchis Fasciolopsis Schistosoma mansoni* and *Schistosoma hematobium* specimens made available by Dr W W Cort *Schistosoma japonicum* specimen courtesy of Dr Henry E Meleney and Dr Harry Most)


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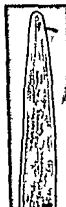

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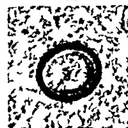

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PLATE XVIII

PLATE XVIII

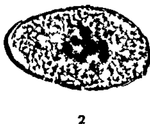
Ova of Helminths

Ova of some of the human helminths and rhabditiform larvae of hookworm and strongyloides (See also Plate XIX)

1 *Ascaris lumbricoides* (unsegmented)
2 *Ascaris lumbricoides* (embryonated)
3 *Ascaris lumbricoides* (segmenting)
4 *Ascaris lumbricoides* (unfertilized)
5 *Ascaris lumbricoides* (decorticated)
6 Hookworm (segmenting)
7 Hookworm (morula)
8 Hookworm (embryonated)
9 Hookworm larva (rhabditiform)
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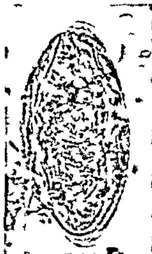
All photomicrographs × 430 Ascaris (segmenting embryonated unfertilized decorticated) hookworm larva (*Paragonimus Clonorchis Fasciolopsis Schistosoma mansoni* and *Schistosoma hematobium* specimens made available by Dr W W Cort *Schistosoma japonicum* specimen courtesy of Dr Henry E Meleney and Dr Harry Most)

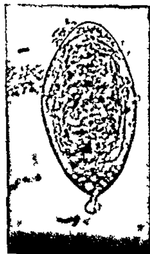

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PLATE XIX

PLATE XIX

OVA OF HELMINTHS

Ova of some of the human helminths (See also Plate XXIII)

1 *Diphyllobothrium latum*
2 *Paragonimus westermani*
3 *Clonorchis sinensis*
4 *Fasciolopsis buski*
5 *Schistosoma mansoni*
6 *Schistosoma haematobium*
7 *Schistosoma japonicum*

temperatures are around 27 C (80 F) but development proceeds at varying rates from about 13 C to nearly 37 C (55 to 98 F) at which point it is inhibited High temperatures such as exist in direct summer sunshine may be fatal to them On clay soil however the moisture content may be sufficient to hold the temperature below the critical level even in the hottest sunshine while on sandy soil the eggs readily perish from the combined action of heat and desiccation The eggs are resistant to low temperatures

Stewart (1916) showed that after hatching in the upper intestine the larvae penetrate the intestinal mucosa enter the veins or lymphatics are carried to the liver and then to the lungs There they penetrate into the alveoli are carried to the mouth with the mucus and only when they are swallowed and again reach the intestine are they able to complete their development This migration requires about ten days during which the larvae moult twice and increase considerably in size Of course many fail to return either becoming lost, being expectorated on arrival in the mouth or being overwhelmed by the immune response of the body Sexual maturity is reached and eggs begin to appear in the stools about two months after infection occurs

EPIDEMIOLOGY

The geographical distribution of *Ascaris* is world wide but the infection is especially common in humid climates A high degree of endemicity occurs only where unsanitary habits prevail

Sanitary facilities restrict the spread of this parasite only when they are used by the entire population The infection is almost always more common among children who are least likely to use the sanitary facilities to be found in primitive living quarters

In most places transmission is effected by hand to mouth transfer of eggs which have been deposited by the children on the floors of the houses or in the immediate vicinity outdoors (Brown 19 7 Cort and Otto 1933) In a very few unusual cases drinking water has been suspected of being the transmitting agent but ordinarily the heavy eggs sink in the water and are not consumed Ascaris eggs can be isolated from market vegetables that have been fertilized by contaminated human feces Cort and Stoll (1931) who found infections unusually widespread among adults in certain regions in China attributed them to this source Winfield and Yao (1937) however found that even when contaminated vegetables were consumed the evidence indicated that house hold pollution was by far the most common source of infection Because pollution in the household is the usual source the infection tends in endemic regions to build up to higher levels in a few families whose habits provide the best conditions for spread

PATHOLOGY

There is little essential pathology in ascariasis During the invasion stages the migration of the larvae produces petechial hemorrhages in the liver and lungs and if large enough numbers pass through simultaneously pneumonia

CHAPTER LXI

THE NEMATODES (ROUNDWORMS) I INTESTINAL WORMS

J ALLEN SCOTT AND Z T BERCOVITZ

ASCARIS LUMBRICOIDES

Ascaris lumbricoides THE COMMON LARGE ROUNDWORM of man is not likely to be confused with any other human parasite on account of its unusually large size and cylindrical form The females usually reach a length of 25 to 30 cm and a diameter of 5 or 6 mm but occasionally they are somewhat larger The males are ordinarily not over 25 cm in length and 4 mm in diameter and can be recognized by the recurved posterior end bearing two short spicules

The eggs are pictured in the section on clinical diagnosis (Plate XVIII) They have a thick shell with a rough albuminous coating which may be lost *by the time they are seen under the microscope They* are normally slightly oval and vary but little in shape and size (60 to 70 by 40 to 50 microns) There are certain eggs however which have vacuolated and degenerate contents and are usually considered to be unfertilized (Plate XVIII) and this type may be distinctly elongated or extremely irregular in shape and size (Otto 193-) When they are passed in the feces the normal eggs usually contain a single well-defined cell although division into two or more cells may occur before they are seen in fecal examinations

LIFE CYCLE AND METHOD OF TRANSMISSION

Development of the eggs is inhibited by the body temperature but as soon as they reach the lower temperature of the exterior environment they begin to develop The development proceeds through certain characteristic stages until a motile embryo can be seen within the shell This embryo very soon becomes an infective larva and will hatch when the egg is swallowed by any mammal although it will only continue to develop in its appropriate host

The heavy shell and the membranes of the normal eggs make them very resistant to environmental changes They are virtually impervious to all chemicals which could be used for the purposes of sterilization Optimum

result from the migration of the adults into the abnormal sites. Anaphylactic reactions in sensitive persons give rise to another group of complications.

DIAGNOSIS

The presence of female *Ascaris* can be readily determined by fecal examinations, since they lay on the average of about [illegible]00,000 eggs a day. A simple smear examination should usually be sufficient, but more precise methods may sometimes be necessary (page 836). Of course a few male worms may be present when the fecal diagnosis is negative. Eosinophilia can be a guide, as in the case of most helminthic infections.

Diagnosis of symptoms in abnormal conditions is difficult, and incorrect decisions may produce dire results. In endemic areas especially it should not be forgotten that these worms sometimes enter the appendix and cause irritation that simulates appendicitis, or that they may actually cause it. They may migrate into the lumen of any duct that opens into the intestine, and they should be kept in mind as a possible cause of symptoms of occlusion. Their rare presence in highly unusual sites throughout the body has usually been discovered during an operation or autopsy, but the fact that this exists may aid in arriving at the correct diagnosis in many obscure conditions. Migration along the intestinal tract commonly causes vomiting, and in such cases the worms may emerge from the nares or enter the larynx, producing severe effects in little children.

TREATMENT

Hexylresorcinol in the form of caprokol crystoids (not in the form of solutions prepared for action against bacterial infections) is recommended for the treatment of ascariasis. The method of administration has been described in the chapter on therapy of helminthic infections (page 842). The use of santonin is not recommended except for certain special cases discussed under the heading of anthelmintic therapy, for it has been proved only mildly effective while it may produce some pronounced toxic symptoms. Chenopodium is considered too toxic to recommend now that an equally effective and entirely safe drug is available. Carbon tetrachloride and tetrachlorethylene are not only ineffective against *Ascaris* but should never be given alone when these worms are present because of the danger of causing them to migrate to other sites or to produce intestinal obstruction.

PROPHYLAXIS

Personal prophylaxis consists in not putting the hands or other unclean objects in the mouth, a difficult thing to teach children unless they are trained not to do it from babyhood. Those who live in regions where the method of fertilizing vegetables is open to suspicion can usually find a way to grow some of their own vegetables or procure them from imported sources. Since chemicals do not affect *Ascaris* eggs, the only effective means of sterilizing fruit is hot water. Even strawberries retain some fresh flavor if immediately put into ice

may result (Koino 1922) It has been long suspected that in endemic regions considerable damage is done to the lungs of children by this passage of the ascaris larvae (Olson Wright and Nolan 1941)

In the intestines the worms remain free in the lumen and cannot be proved to do any real damage under ordinary conditions such common symptoms as colic and nervous manifestations being ascribed to mechanical irritation which does not lead to the formation of lesions There is a vast literature however on the serious pathologic conditions resulting from intestinal obstruction by balls of worms as well as from worms which have migrated into abnormal sites It should be emphasized that these are unusual conditions and have been extensively discussed because of that fact Their seriousness should not be overlooked and especial note should be made of the fact that some drugs produce these effects (page 789)

Many persons are sensitive to the excretions or the body fluids of *Ascaris* symptoms of anaphylactic shock often occurring in laboratory workers who handle the worms The nervous and toxic symptoms seen in patients harboring these worms may also be due to this sensitivity

SYMPTOMATOLOGY

Symptoms of the passage of larvae through the lungs may be pronounced in patients who have swallowed large numbers of eggs Among the usual cases seen in endemic areas there are undoubtedly many with noticeable lung symptoms resulting from the larval migration but it is impossible to be certain that this is the cause in most cases

Many children harbor *Ascaris* and show no symptoms The commonest symptoms noted among these are probably those associated with mild intestinal irritation To a certain extent the degree of irritation is correlated with the number of worms present but this is by no means always true When the infection is heavy children suffer considerably from a wide variety of abdominal complaints In some instances this varies from mild colic to severe cramps with nausea vomiting and even intestinal obstruction due to a bolus of worms The nausea and vomiting is not infrequently associated with passage of worms into the esophagus and mouth or through the nose Occasionally the worms enter the larynx Ascarids have been found in the appendix and have caused intestinal perforation and hemorrhage especially in cases of typhoid fever In many instances there is loss of appetite malnutrition and irritability Disturbed sleep reflex muscular contractions indigestion loss of appetite and general fretfulness are often eliminated when the worms are exterminated but in most cases in endemic areas little or no symptomatology can be elicited

COMPLICATIONS

Complications with ascariasis are numerous Girges (1934) for example lists as many as twenty one Fortunately they are all of rare occurrence Appendicitis and pseudo appendicitis perforation of the intestinal wall and intestinal obstruction are included in the list as well as the many conditions which may

on to the region of the cecum where they attach and complete their development From the time the eggs are swallowed about three months elapse before the worms are mature and start laying eggs

EPIDEMIOLOGY

Trichuris is primarily a parasite of warm countries but it is endemic in some northern European regions under unexplained conditions As a rule it is not found except where *Ascaris* is present but does not occur everywhere that *Ascaris* does on account of the greater sensitivity of the *Trichuris* eggs to temperature and moisture variations (Spindler 1929a) *Trichuris* is not found in colder and drier regions The human habits associated with epidemiology of *Trichuris* are apparently exactly like those associated with *Ascaris* and the heaviest cases are also apt to appear in certain families (Cort and Otto 1937)

PATHOLOGY

In most persons relatively few worms are harbored and there is no essential pathology The anterior part of the worm is embedded in the mucosa but there is ordinarily no tissue reaction beyond a liquefaction of the cells in that area (Hoeppli 1933) When many worms are harbored there may be a slightly greater degree of cellular reaction These areas may become secondarily infected with resulting inflammatory reaction This type of reaction sometimes occurs in the appendix

SYMPTOMATOLOGY

Most persons infected with *Trichuris* show no symptoms Some children have indigestion sleeplessness irritability and other nervous conditions which have been attributed *to these worms* but *the etiologic relation is not firmly* established

COMPLICATIONS

Complications depend on the rare possibility that the worm may give access to secondary invaders or cause appendicitis

DIAGNOSIS

The presence of *Trichuris* can be demonstrated readily by fecal examination but these worms lay relatively few eggs so that a more exhaustive search is necessary than in the case of *Ascaris* or hookworm The presence of eggs does not indicate that any symptoms present are due to these worms and differential diagnosis based on symptomatology is difficult if not impossible in most cases

TREATMENT

The only drug which has a satisfactory effect on these worms is *leche de higueron* but it can be obtained only in certain parts of the world since no satisfactory method of preservation is known The use of this drug is described

water after being dipped in boiling water *Ascaris* eggs and amebic cysts although resistant to chemicals which would kill bacteria do not resist temperatures of approximately 55 C (130 F) for more than a few seconds Of course they must actually be raised to this temperature and therefore generous allowance for the cooling effect of the fruit to which they are attached must be made

Public prophylaxis or control of ascariasis depends on adequate sanitation which is used approximately 100 per cent Cort (1931) has emphasized the need to have privies built near the house so that the children can be persuaded to use them and to have them constructed with seats for children Education is of prime importance Sanitation which is physically satisfactory may fail to control ascariasis simply because few children in the family do not use the facilities provided Treatment as a means of control is of no value for these worms seldom live more than a year and the normal turnover is so great that new worms are acquired soon after treatment has been given

TRICHURIS TRICHIURA

Trichuris trichiura has recently been officially recognized as the correct name for human whipworm replacing the name *Trichocephalus trichiura* The shape of the adult worms is such that they can be easily distinguished from all other human parasites The anterior three fifths of the worm is a thin threadlike capillary tube containing only the esophagus The remainder of the worm is about ° mm in diameter and contains the rest of the digestive system and reproductive organs The entire worm is usually about 30 to 50 mm long the females averaging slightly longer than the males The males can be distinguished by the coiled posterior portion from which a single spicule extends

The eggs (Plate XVIII) have a characteristic elliptical shape with a clear plug at each end They vary slightly in size but usually are about 50 by 22 microns

LIFE CYCLE AND METHOD OF TRANSMISSION

The adults usually live in the cecum but may also occasionally be found in the appendix the colon or the ileum The life cycle is much like that of *Ascaris* except that the larvae do not migrate after hatching Like *Ascaris* the eggs of the whipworm offer great resistance to chemicals and to unfavorable environmental conditions in general They are not however resistant to low temperatures as *Ascaris* is (Nolf 193°) and they are more sensitive in their moisture requirements (Spindler 19 9a Oronato 1931) They develop at a slower rate than *Ascaris* for Brown reported (19 7) development of *Trichuris* eggs in twenty-one days as compared to fifteen days for *Ascaris* under similar conditions Like those of *Ascaris* the eggs are not infective if swallowed before they have passed through this developmental stage When swallowed after they become infective they hatch in the intestine (Miller 1939) and the larvae hide in the crypts of the small intestine for ten days before they move

in some other regions it occurs alone while in the Mediterranean region and some parts of the Orient *A duodenale* is found alone A third species *A braziliense* which is primarily a parasite of cats and dogs occasionally occurs in man but it is of no special clinical significance The important role of this species in the production of the skin lesions known as creeping eruption will be discussed elsewhere (page 796)

LIFE CYCLE AND METHOD OF TRANSMISSION

The adult hookworms live in the duodenum and attach themselves to the mucosa from which they continuously suck blood Their length of life is variable the great majority being lost within a year or two In several instances persons infected with a few worms have moved to a locality where further infection was impossible but the eggs continued to appear in the stools for as long as seven years

The females lay thousands of eggs daily which pass with the human feces onto the soil The embryonic development is rapid and under favorable conditions of temperature and moisture the larvae hatch out within about twenty four hours The newly hatched larvae measure on the average 0 25 mm in length and bear a close resemblance (Plate XVIII) to the rhabditiform larvae of *Strongyloides stercoralis* but may be differentiated from them by their longer and narrower buccal cavity By the third day the larva undergoes its first moult Growth then continues the character of the esophagus changes and becomes slender and filariform in appearance The second moult then occurs when the larvae become infective organisms

Once having reached the infective stage the larvae may remain alive for several weeks or even longer if the conditions continue to be favorable Adverse conditions such as hot sunlight or a rapidly drying soil may kill off many larvae while shade and constantly moist soil favor their development and persistence They develop much more readily in a sandy soil than they do in a clay soil In a loose soil the larvae will migrate downward an inch or so if the upper layers slowly dry and will return to the top when it is again moistened Too much moisture is inimical however and the larvae are seldom found developing in areas where the soil is constantly saturated They do not migrate laterally to any extent and consequently the infective spots are those where pollution has occurred a few weeks previously The larvae migrate vertically for some distance if covered by loose soil

If the infective larvae are brought into contact with the human skin for a few minutes they are able to penetrate it actively even though it is unbroken This penetration probably occurs most frequently when mud containing the larvae adheres to bare feet or to the hands of agricultural workers for the larvae apparently need something against which they can push in making the first break into the skin Infection by mouth can take place though it is probably rare

Once in the skin the larvae enter the blood vessels and are carried with the blood to the heart and then to the lungs where they are stopped in the capillary

in the chapter on therapy (page 851) Elsewhere hexylresorcinol in the form of caprokol crystoids is probably the best and most convenient substitute It is said to remove from 30 to 50 per cent of the worms from most cases (Brown 1934) Repeated treatment may or may not be more effective depending in all probability on the position of the worms Faust (1931) recommends a saline purge followed by tepid high enemas then the usual full dose of tetrachlorethylene the entire course to be repeated several times at weekly intervals

PROPHYLAXIS

Personal prophylaxis is similar to that for *Ascaris* namely avoidance of putting hands and contaminated objects in the mouth and care in the use of green vegetables in countries where human feces are used as fertilizer Public prophylaxis or control can be achieved by sanitation only when the youngest children are educated to use the facilities provided

HOOKWORM DISEASE

Adult hookworms which live in the small intestines are about one half inch long and on first glance look like a smooth piece of rather thick white cord On closer examination a globular buccal cavity can be seen while the posterior end of the male is seen to be provided with a conspicuous copulatory bursa. The common human hookworms are of two species *Ancylostoma duodenale* and *Necator americanus*

Differentiation of the species can be made only by examination of adult worms recovered at autopsy or removed from stools after treatment

MORPHOLOGY

A duodenale is characterized by its well developed buccal capsule with two pairs of curved teeth on the ventral wall which are equal in size and one pair of dorsal teeth or triangular plates The male measures from 8 to 11 mm in length by 0 4 to 0 5 mm in breadth The female measures from 10 to 13 mm in length by 0 16 mm in breadth

N americanus has a smaller mouth capsule than *A duodenale* and the two pairs of curved ventral teeth characteristic of the latter species are replaced by a pair of ventral cutting plates *N americanus* is also smaller than *A duodenale* The male measures from 7 to 9 mm in length and is about 0 3 mm in diameter The female measures from 9 to 10 mm in length and from 0 3 to 0 4 mm in diameter The eggs are practically indistinguishable from those of *A duodenale* They are oval in shape and have a thin transparent shell (Plate XVIII) When freshly deposited they contain two to four and rarely eight blastomeres each but by the time of examination often contain fully developed embryos They vary considerably in size measuring from 56 to 60 microns in length by 34 to 40 microns in breadth

In many parts of the world the two species are found together but *N americanus* is usually the predominating species In the United States and

in some other regions it occurs alone while in the Mediterranean region and some parts of the Orient *A duodenale* is found alone A third species *A braziliense* which is primarily a parasite of cats and dogs occasionally occurs in man but it is of no special clinical significance The important role of this species in the production of the skin lesions known as creeping eruption will be discussed elsewhere (page 796)

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bed They penetrate into the alveoli and are carried with the mucus to the mouth frequently causing a transient cough Some of them are probably spit out but others are swallowed and when they reach the intestine they begin to grow attach themselves to the intestinal wall and in about six or eight weeks are sufficiently mature to begin laying eggs

EPIDEMIOLOGY

The epidemiology of hookworm disease has been summarized by Chandler (1929) and Cort (1932 1941) The geographical distribution of hookworm disease is limited in general by temperature and rainfall and locally by the sanitary habits of the people and the types of soil Except for special conditions such as those prevailing in mines it does not exist outside the limits of about 36 degrees north latitude and 30 degrees south Since the larvae in the soil will not develop at temperatures near freezing transmission does not occur under winter conditions Outside the tropical and subtropical belt the season in which the temperature would favor transmission is usually too short to keep a generalized infection established in the population Within this belt of favorable temperature conditions the infection does not ordinarily occur in severe form unless the rainfall is at least 40 inches a year The character of the soil also limits the distribution markedly because the larvae do not find favorable conditions for life in clay soil Hookworm infection is not endemic in cities where adequate sanitary facilities are provided and its spread else where is often limited by sanitary habits and by high economic standards which permit the wearing of shoes

PATHOLOGY

Although hookworm disease occasionally occurs in acute forms it is com monly a chronic disease of varying severity In general the severity of the disease depends on the number of worms harbored by the patient the length of time he has borne them and his ability to compensate for their debilitating effects The most characteristic pathologic manifestation of hookworm disease is anemia Apart from the anemia and its attendant effects the pathology con sists primarily of damage to the intestinal mucosa from the biting worms Occasionally lesions so produced are large and ulcerated but as a rule they are of relatively minor importance

The anemia appears to be produced solely by chronic blood loss and is usually associated with a state of iron deficiency or chronic malnutrition Well nourished persons unless very heavily infected are apparently able to compen sate for about as many worms as they acquire Even undernourished persons may be able to compensate for a few hookworms over long periods of time or for the effects of a larger number for a short period Apparently the break down comes when the iron reserves are so depleted that regeneration of blood cannot keep up with the loss and as a result anemia begins to develop (Rhodes Castle Payne and Lawson 1934 Suarez 1933) Rhodes and others found that the addition of iron to the diets of Puerto Rican hookworm patients produced

a reticulocyte response and a marked rise in the hemoglobin level even though no attempt was made to remove the worms They state however that their patients diets were not as deficient in iron as they were in animal proteins and vitamins A B and D Others including Payne and Payne (1940) and Otto and Landsberg (1940) have also indicated that animal proteins minerals and vitamins all play an important part in this picture

The pathologic changes in the skin resulting from the penetration of the larvae start with itching local edema and erythema and are followed in many cases by the formation of vesicles and sometimes by a more generalized urticarial rash Scratching frequently leads to secondary pyogenic infections which produce the typical clinical picture known as ground itch Microscopically the local inflammatory reaction resembles any response to a foreign body and a toxic agent except that an unusually large number of eosinophiles a common response to most helminth parasites and toxins are present

SYMPTOMATOLOGY

The symptoms of skin penetration of hookworm larvae are usually recognized only after the intestinal stage has been established The lesions are not easily differentiated from those following insect bites or the penetration of schistosome cercariae except for the fact that ground itch is most common between the toes Likewise coughs bronchitis or pneumonitis cannot be definitely attributed to hookworm except by inference after it is known that infection has occurred

Anemia is of course the most noticeable symptom and is often associated in severe cases with yellowing of the skin and a generalized edema giving the patient a characteristic appearance In most cases the blood loss is well compensated for a time and the clinical cases are found among those with a large number of worms or those whose compensatory mechanism has broken down under the continuous drain over a long period of time In every group of infected persons there are always some who have too few worms to cause symptoms

Long standing chronic and repeated infections can produce effects of much more profound nature Retardation of growth as well as backwardness in scholastic attainment on the part of infected children has been demonstrated Mention should also be made of the classic picture of laziness and indolence though it is doubtful whether the hookworm infection is the sole cause in many of these cases In extreme cases there may also be a history of rheumatoid muscular pains some cardiac disturbances nervous symptoms such as those expressed in the habit of dirt eating and a retardation or disturbance in the development of the primary or secondary sexual functions and characters It should not be forgotten however that the classic picture of severe hookworm disease was drawn before there was sufficient recognition of the effects of malnutrition accompanying the disease Consequently special care is necessary in the interpretation of symptoms It seems probable that the characteristic syndromes are produced by the combined effect and that the whole picture should be looked upon as an entity

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The anemia appears to be produced solely by chronic blood loss and is usually associated with a state of iron deficiency or chronic malnutrition Well nourished persons unless very heavily infected are apparently able to compensate for about as many worms as they acquire Even undernourished persons may be able to compensate for a few hookworms over long periods of time or for the effects of a larger number for a short period Apparently the break down comes when the iron reserves are so depleted that regeneration of blood cannot keep up with the loss and as a result anemia begins to develop (Rhodes Castle Payne and Lawson 1934 Suarez 1933) Rhodes and others found that the addition of iron to the diets of Puerto Rican hookworm patients produced

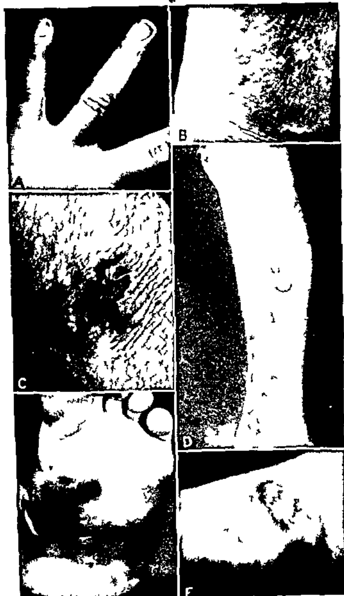


Fig 06 Creeping er pt on on extrem t es A Les on on r ng fing r B Linear lesion on dorsu n of v r t c B lla on fo earm D Few rem ning a tive les ons on leg following treat ment E. Clo e up v ew of les n on foot showing nfiltration and bullae F M grat on across plantar surface of foot w th bulla and infiltrat on (Kirby Sm th Dove a d Wh te *Ir hives of De m tology and Syphilology*)

DIAGNOSIS

The presence of hookworm eggs in the stool is diagnostic of infection but it should not be forgotten that worms may be present without doing any appreciable harm The mistake is often made of treating a patient for hookworm disease simply because eggs are present in the stool when the real cause of his illness should be sought elsewhere The laboratory examination does not eliminate the need for differential diagnosis Only a very rough approximation of the number of worms is possible by egg counting methods when they are applied to individuals especially if only one fecal specimen is counted but even this knowledge can be of great help to the clinician When relatively large numbers of eggs are being passed and when other causes of anemia can be ruled out it is reasonable to assume that the hookworms probably represent the cause of the anemia

TREATMENT

In the treatment of hookworm disease tetrachlorethylene and hexylresorcinol have become the drugs of choice by nearly all physicians who have had adequate experience (For dosage and methods of administration see page 84)

In view of the relation of malnutrition to hookworm anemia some form of iron therapy and an improved diet are indicated to hasten recovery from the anemic state after the removal of the hookworms When the anemia is severe it is often dangerous to subject the patient to the violent shock of anthelmintic treatment with its accompanying purgation Such cases should be put on some form of iron therapy to build them up so that they can stand the anthelmintic treatment

PROPHYLAXIS

The wearing of stout shoes and the avoidance of contact of the hands with possibly polluted soil either in agricultural work or elsewhere makes personal prophylaxis almost perfectly efficient Community prophylaxis is more difficult however as the co operation of nearly 100 per cent of the population is necessary Successful campaigns for the control of the disease are based on the provision of sanitary privies of a type that the local population will actually use when urged to do so by an educational effort Treatment of all infected persons in the community is a valuable adjunct in bringing down the level of infection at the start and is better than waiting for the slower effect of sanitation alone It also serves to stimulate interest through a demonstrable removal of worms and an evident improvement in the health of some persons Treatment alone is of doubtful prophylactic value but may be useful in keeping the population in better health until real prophylactic measures can be instituted

CREEPING ERUPTION

The larvae of certain cat and dog hookworms which only rarely mature in the human intestine frequently penetrate the human skin and migrate just beneath the skin (Fig 106) causing a linear eruption The characteristic of these eruptions is that they migrate in a line which progresses at o end The

the larvae of hookworms enter the blood vessels and pass to the heart and then the lungs In the case of *Strongyloides* considerable development occurs here the males becoming mature and fertilizing the adolescent females before they migrate to the trachea and to the intestine (Faust 1933 1935) Under certain conditions of massive infection the females may mature in the lungs and the larvae hatching from their eggs may cause hyperinfection Ordinarily the females go on to the intestine and become embedded in the mucosa before they mature and lay their eggs The males apparently do not linger in the intestine but once they leave the lungs they rapidly leave the body There is still some controversy over the details of this part of the life cycle especially with regard to the necessity for fertilization of the parasitic females by the males In the *Strongyloides* of the rat no males are necessary as infection can be established under controlled conditions by a single infective larva (Graham 1936)

Hyperinfection due to autoinfection or internal reinfection has long been considered a possibility and seems to finally have been clearly demonstrated by the work of Faust and de Groat (1940) who found the developing stages in the mucosa at autopsy That it can occur in the lungs as aforementioned also seems to be likely These cases of hyperinfection are relatively rare but are the ones displaying the most destructive pathology

PATHOLOGY

The larvae of *Strongyloides* passing through the skin produce lesions similar to the ground itch of hookworm while the effects on the lungs and the production of coughs are essentially the same While becoming established in the intestine the young worms cause a more or less severe inflammation The worms as they mature continue to tunnel through the mucosa and cause a considerable degree of mechanical damage Faust (1935) who has made a thorough study of the pathology in dogs states that lytic action also plays a considerable part in the total picture of destruction As the cases become chronic a tissue reaction occurs involving phagocytosis of the worms as well as fibrosis of the middle and lower portion of the glands compensated by hyperplasia of the tips of the villi In some dogs and apparently quite often in human beings this reaction does not take place with sufficient rapidity and as a result the entire mucosa may become necrotic and denuded

As a rule the infection is established in the duodenum and jejunum but it is not rare to find the parasite in any other part of the intestine where the tissue reaction differs only by reason of the different cells present Like *Ascaris* these parasites occasionally wander into the gall bladder the lungs or other organs of the body and unlike *Ascaris* *Strongyloides* is able to establish itself in these abnormal sites and continue life in them

SYMPTOMATOLOGY

The *symptoms* of strongyloidiasis are not constant and many infections apparently give rise to no symptoms Abdominal pain of varying types and in

larvae are usually just ahead of the visible lesion and therefore their exact position cannot always be determined Lesions caused by several larvae may be intermingled They occur most commonly on the legs of children who play on beaches or in sandy soil under houses They have also been found to be common on the backs of plumbers and other workmen who lie on the sandy soil while making repairs under the floors of houses Diagnosis can be easily made because of the linear character of the lesion The treatment consists of freezing a spot just in front of the advancing end of the lesion with ethyl chloride Prophylaxis consists of avoiding contact with sandy places where cats and dogs may possibly have polluted the soil

STRONGYLOIDES STERCORALIS

The parasitic females of *Strongyloides stercoralis* are usually slightly over 2 mm in length and vary in diameter from about 30 to 75 microns They live deeply embedded in the intestinal mucosa especially in and between the glands of Lieberkuhn They are seldom seen except at autopsy The males have been seen only by a few observers after careful search and closely resemble the free living males of this species to be described below The eggs which resemble those of hookworms are laid deep in the mucosa and except in the case of violent diarrhea or after strong purgation they are not seen in the feces The larvae hatching from the eggs are about 200 microns in length but by the time they are seen in the feces they have usually passed through one moult and are about 500 to 600 microns long They resemble the rhabditoid larvae of hookworm (Plate XVIII) but can be distinguished from the latter by their short buccal vestibule and larger genital primordium

LIFE CYCLE AND METHOD OF TRANSMISSION

Strongyloides infections are occasionally continued by autoinfection or hyperinfection as it is sometimes called but ordinarily these worms must pass through a part of the life cycle in the soil just as is the case with hookworms In the case of *Strongyloides* there are interesting variations possible in the free living portion of the life cycle The larvae in the feces may develop much as hookworm larvae do into filariform infective larvae capable of penetrating the skin and causing human infection Under other circumstances perhaps of an environmental character (Beach 1936) the larvae develop into a free living generation of adult males and females The males were described by Kreis (1932) and Faust (1933) The females are smaller than the parasitic females being about 1 mm long and 60 microns in diameter After fertilization these females lay eggs from which hatch larvae which develop into filariform infective larvae exactly like those developing directly from the larvae in the feces These two modes of development are called the direct and indirect methods respectively and may occur simultaneously in the same fecal cultures Under experimental conditions at least the indirect cycle may repeat itself several times in culture before the infective stage is produced (Beach 1936)

The infective larvae however they may develop penetrate the skin as do

especial care has been taken to record its presence The highest frequency on record is that of approximately 20 per cent in a Panama group (Faust 1931)

PROPHYLAXIS

Since so little is known about the epidemiology recommendations as to prophylaxis can only be based on those of hookworm Since *Strongyloides* is less resistant to environmental changes sanitation should theoretically have a more effective response but this is not necessarily true Personal prophylaxis consists in wearing shoes and in avoiding contact with contaminated soil in agricultural work

ENTEROBIUS VERMICULARIS

Enterobius vermicularis (oxyuris or pinworm) is a small worm the anterior extremity of which is surrounded by a cuticular expansion The mouth is surrounded by three fairly distinct lips and the esophagus is provided with an extra or prebulbar swelling and a distinct bulb The male is much smaller than the female and measures from 2 to 5 mm in length The female worm measures from 9 to 12 mm in length and has a long pointed tail The uteri in gravid specimens are greatly distended and these give a plump appearance to the body The eggs are characteristically asymmetrical and contain a more or less fully developed embryo when deposited by the female A short period is required for the larvae to become infective after they leave the worm The eggs (Plate XVIII) vary from 50 to 60 microns in length and 30 to 32 microns in breadth The shell is hyaline relatively thick and encloses the embryonic membrane

LIFE HISTORY AND METHOD OF TRANSMISSION

Infection with *Enterobius* occurs through the swallowing of eggs containing infective larvae which then hatch in the stomach or intestine For a few days these larvae are found in the lower part of the small intestine the cecum or the upper part of the colon where they pass through a series of moults During the final larval stage they apparently sometimes penetrate the intestinal mucosa since Chitwood has found them in the epithelium of the appendix (Chandler Alicata and Chitwood 1941) When they become adult they are found only in the lumen of the intestine Copulation occurs there and the males apparently remain at the site for some time The females mature all their eggs at the same time but without laying any of them they start a downward migration along the intestine Passing out of the anus and crawling onto the skin of the perianal region they begin to deposit the eggs The period from the swallowing of the eggs to the appearance of the mature females is not less than fifteen days Some of the worms are passed in the feces but under circumstances of modern urban life at least these play no part in the epidemiology It is one of the peculiarities of the life history of *Enterobius* that the eggs are normally not laid in the intestinal lumen but only after the female has left the body

varying locations is the most common symptom according to Hinman (1938) who has given the best review of recent clinical findings There is no evidence that light cases are always innocuous as is the rule in hookworm infection but the severe symptoms are usually found in cases with heavy infection Diarrhea is the most noticeable severe symptom It is often violent and intractable and severe dysentery may ensue As a rule diarrhea has a tendency to remission and recurrence and may last for years without severely affecting the health of the person infected but again may rapidly become worse and produce fatal results The symptoms of infection in the lungs resemble those of other types of bronchitis and pneumonitis

COMPLICATIONS

There are no true complications involved in *Strongyloides* infections except that the manifestations of extra intestinal infection are naturally atypical

DIAGNOSIS

Since the females produce very few eggs each day it may be difficult to discover the larvae in the stools even in heavily infected cases Repeated examinations are necessary then before a negative finding is reported Methods of examination are discussed elsewhere (page 836) Like most helminth infections *Strongyloides* gives rise to an eosinophilia which may be a helpful sign pointing to continued fecal examinations although Faust (1936) states that as cases become chronic the eosinophilia decreases and the early leukocytosis is replaced by leukopenia

TREATMENT

Of the many drugs given for this infection only gentian violet has proved consistently satisfactory It is usually given in tablet form but can be given to refractory cases by duodenal tube or intravenously to those with infections in organs other than the intestine Faust (1941) who has probably had the most experience with this treatment recommends that after treatment stool examinations be made by concentration techniques for three to six months to make sure a cure has been effected

EPIDEMIOLOGY

Relatively little is known of the epidemiology of strongyloidiasis Since infection occurs in the same manner as that of hookworm many aspects of the epidemiology must be the same The free living larvae of *Strongyloides* are much more delicate and sensitive to environmental influences than are those of hookworm and this may account for the fact that the former parasites are found less frequently than the latter (Cordi and Otto 1934) Hinman (1938) has reviewed the literature on the prevalence of infection and concludes that it occurs in the southern United States in from 1 to 5 per cent of the population Since it is not usually diagnosed in routine fecal examinations made for survey purposes the only information available is contained in studies in which

especial care has been taken to record its presence The highest frequency on record is that of approximately 20 per cent in a Panama group (Faust 1931)

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Another unusual feature is that the eggs already contain larvae when passed on the perianal skin and these larvae become infective in a very short time after leaving the adult worm (six to seven hour at body temperature) The eggs may remain viable for about ten days outside the body

It is clear then that under these conditions an infection will automatically die out unless reinfection constantly occurs The irritation of the migrating worms at night induces scratching of the anus It has been shown moreover that viable eggs are *apparently shaken from the bedclothes* and blown about in the dust of the house for they have been recovered from such unlikely places as the tops of doors and picture frames (Nolan and Reardon 1939) Introduction of eggs into the mouth from the hands produces reinfection and contamination of the food of others may start new infections It is thus easy to see how infection spreads through a family or may be carried by an occasional visitor to a new family In the tropics and subtropics at least the eggs can be regularly found in the dust on the floor or on the ground surrounding the houses (Headlee 1933 1936) Once established infection is apparently maintained and intensified principally by reinfection of the individual from the eggs of his own worms

PATHOLOGY

Extended discussion of the role of *Enterobius* in the causation of appendicitis may be found in the literature on the subject but the consensus of present conservative opinion is that it is not a causative agent in this disease The worms are frequently found in the lumen of pathologic appendices but their presence is merely one of chance and no etiologic relationship is indicated Brady and Wright (1939) are of the opinion that worms are not found in the appendix as often as would be expected in light of their prevalence in the general population The pathologic effect of these worms is apparently very slight

SYMPTOMATOLOGY

Brady and Wright (1939) have provided the best available information on the symptoms to which the worms give rise since they were able to check their findings against similar observations in uninfected control groups

The most common symptom is *pruritus ani* and apparently most of the other symptoms are usually secondary to this Wright Bozicevich and Gordon (1938) found that the degree of distress was usually more nearly correlated with the temperament of the patient than with the number of worms passed after treatment Many stolid phlegmatic individuals disclaimed any sensations whatever from the migrating worms In the rest the sensation varied from a mild tickling to an intolerable itching and severe dermal irritation

Numerous gastro intestinal symptoms have been attributed to pinworm infection but it is doubtful whether there is an etiologic connection in many reported cases Brady and Wright (1939) found that abdominal pain of undetermined origin did not occur more frequently in their infected group than

in the non infected They attribute other gastro-intestinal symptoms to the infection although they state that their control group was not large enough to substantiate their opinion

Enuresis is commonly mentioned as occurring in pinworm infection but Brady and Wright did not find it more common in their infected than in the uninfected group They observed however that the migrating worms frequently enter the vulva and probably often cause vaginitis They think a purulent vulvovaginitis may sometimes result from organisms carried into the vagina by the worms Cases are also on record of female worms encysted in the peritoneum and fallopian tubes with accompanying symptoms similar to those of bacterial infections at the same sites Obviously the worms reached these places by passing through the uterus

DIAGNOSIS

The recovery of eggs or female worms from the perianal region is the most satisfactory means of diagnosing enterobiasis Eosinophilia if present is slight and gives no significant clue Only a small proportion of the cases is found positive on routine fecal examinations even if concentration methods are used When entire stools are kept over night in closed containers in a warm place the worms will often be found on the upper surface in the morning Scrapings from finger nails reveal many positive findings but recovery of eggs or female worms from the perianal region is the only sure method of diagnosis

With the devices now available perianal scrapings are easily obtained The NIH (National Institute of Health) swab and one recently introduced by Graham are described elsewhere (page 840) Only the former has had extensive use and it has been determined that at least seven consecutive daily swabs must be made to reveal 99 per cent of the positive cases but swabs made on two days will reveal 90 per cent (Cram Jones Reardon and Nolan 1937 Sawitz Odum and Lincicome 1939) Since the worms are more apt to migrate at night swabs must be made in the morning before bathing or before evacuation of the bowels These swabs can be easily made in the physician s office and sent to the home to be used by the individual himself or by the mother of children Since the treatment seldom produces permanent effects unless given simultaneously to all members of the family the physician should provide a swab for each member each day Swabs from the vulva obtained without touching the exterior portions can be useful in checking the possibility that vaginitis is due to the presence of these worms

TREATMENT

Recent work has shown that persistent treatment is necessary to kill the young worms as they mature and that this can best be given by daily doses over a long period of time The eggs probably do not live more than two weeks in the ordinary household environment and a prolonged or intermittent treatment should obviate infection from eggs passed after treatment has begun Gentian violet is standard for this purpose and is tolerated by most persons

Another unusual feature is that the eggs already contain larvae when passed on the perianal skin and these larvae become infective in a very short time after leaving the adult worm (six to seven hours at body temperature) The eggs may remain viable for about ten days outside the body

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(For details of administration of gentian violet see page 847) The patient takes tablets before meals for eight days omits them for a week and repeats for another eight days The physician must insist on the entire course being taken and then check the results by seven consecutive daily swabs

Many physicians are now insisting that all infected persons in the family must be treated simultaneously They refuse to treat one individual alone for they have found that reinfection occurs so regularly in families with other infected persons that treatment might as well not have been given Rigid prophylactic measures may be of value if carried out by all infected members of *the family during the treatment period These measures consist* of wearing tight panties or shorts day and night changing them at least every morning and on removal dropping them into a pail of water Then the entire anal region should be washed and the cloth also put in the pail as well as the bed sheets and night clothes which should be carefully folded to avoid shaking out any eggs The water in the pail should be brought to boiling to insure that every portion reaches a temperature of 65 5 C (150 F) Particular care should be given to washing the hands and scrubbing the nails especially in the morning and before food is handled Toilet seats should be frequently washed and some means used to prevent children from touching other possibly contaminated objects Experience has shown that the infection persists tenaciously in a family and that only a concerted effort will uproot it

EPIDEMIOLOGY

The prevalence in institutions tends to be higher than in the general population sometimes approaching 100 per cent (Sawitz Odum and Lincicome 1939) In studies in Washington (Bozicevich 1937 Cram Jones Reardon *and Nolan 1937 Bozicevich and Brady 1938) in a town near Quebec* (Miller and Choquette 1940) and in North Carolina (Brown Sheldon and Thurston 1940) about one third of the groups examined were found infected on the first swab examined Additional swabs made in some series indicate that the true prevalence would probably have been more than 50 per cent Most of these persons were from the lower economic classes and the work of the last mentioned authors indicates that the prevalence in more prosperous groups is very much lower

If one member of the family becomes infected there is a tendency for the infection to spread to many other members and the prevalence seems to be highest in large families

PROPHYLAXIS

General cleanliness and care in the handling of food are the best means of prophylaxis known Symptomless infected members should be treated as a prophylactic measure in the interests of others in the family Treatment in schools of infected children and their families may be a reasonable form of prophylaxis but in most institutions little has yet been done to demonstrate that prophylactic treatment can be made effective

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bed they arrive in the systemic circulation Once in the arterial blood they are carried to all or nearly all of the voluntary muscles of the body The young worms are most numerous in the blood stream from the eighth to twenty fifth days after infection The interval between infection and muscle penetration is somewhat variable Larvae may begin to reach the muscles by the ninth or tenth day after infection but are difficult to find before the fifteenth day

Data concerning the number of larvae produced by a single female worm are variable In rats the average seems to be between oo and 300 McCoy estimated a production of about 1 500 per female in monkeys and Roth found 1 000 to 500 in guinea pigs

After reaching the voluntary muscles (Fig 107) the larvae penetrate the sarcolemma and come to rest within the substance of the muscle fiber Here they undergo rapid growth Within ten days or two weeks after penetration they reach a length of approximately 1 mm and become spirally coiled These infective larvae may be found as early as twenty one days after infection Marked degenerative changes occur in the muscle fibers and in four to six weeks a membranous capsule begins to form around the worm Usually each of these ovoid lemon shaped cysts contains a single coiled larva but occasionally two or more larvae may be found in the same cyst Calcification of the cyst wall begins to take place usually in about eight to ten months although several years may be required for complete calcification In time the larvae die and are absorbed or become calcified Their longevity is variable Live larvae capable of infecting other animals have been demonstrated in a hog kept for eleven years under conditions which precluded reinfection

Most investigators have found that infection cannot be transmitted through the placenta Roth using guinea pigs is apparently the only worker who has reported such transmission However Kuitunen Ekbaum reported the finding of live larvae in a human fetus of seven months term

EPIDEMIOLOGY

The parasite is widely distributed in many hosts Cats dogs and rats are frequently infected In addition to infection from pork clinical cases in man have resulted from the consumption of smoked dog meat the flesh of the nutria and bear meat

Infection in swine varies with methods of husbandry type of food and presence or absence of control measures In the United States hogs usually become infected from pork scraps in garbage the rat being a relatively minor factor in the transmission of the disease to swine In Canada where the cooking of garbage is required Cameron found only 0 ,5 per cent of 2 000 hogs infected In European countries for which data are available the incidence in swine is only a fraction of 1 per cent many of these countries require the microscopic inspection of pork and the condemnation or processing of infected carcasses

High incidences are recorded from swine in the United States In the United States Bureau of Animal Industry studies reported on first by Hall and later

CHAPTER LXII

THE NEMATODES (ROUNDWORMS) II TISSUE WORMS (TRICHINOSIS)

WILLARD H WRIGHT AND Z T BERCOVITZ

TRICHINOSIS IS A CLINICAL CONDITION CAUSED BY THE invasion of the body by the adults and larvae of the nematode parasite *Trichinella spiralis*

ETIOLOGY

Trichinella spiralis (Owen 1835) Railliet 1895 belongs in the nematode superfamily TRICHINELLOIDEA Hall 1916 and the family TRICHINELLIDAE Ward 1907 The sexes are separate The body is slender somewhat attenuated in the anterior portion and slightly thicker posteriorly The male is from 1 4 to 1 6 mm in length and from 0 04 to 0 05 mm in diameter It is provided on the posterior extremity with a conical projection on either side of the protrusible cloaca but is without a spicule The female is from 3 to 4 mm in length and approximately 0 1 mm in diameter The vulva is anterior to the junction of the esophagus and intestine

Life history The mature worms occur mostly in the small intestine and the infective larvae in the striated or voluntary muscles of the same individual When the individual consumes muscle tissue containing viable infective trichina larvae the larvae are freed from their cysts by the action of the gastric juice and migrate from the stomach to the small intestine Here the sexes *develop to maturity usually within seventy two hours and mate* promptly In laboratory animals birth of living young begins to take place as early as the fourth day after infection Larval production may continue for a period of six weeks or longer

At birth the young worms measure about 0 1 mm in length and 0 006 mm in width The body is of nearly uniform diameter throughout An oral spear is present but the digestive tract is very rudimentary and is characterized by an undifferentiated cellular structure The young larvae find their way to the lymph spaces and are carried to the thoracic duct from which they reach the venous circulation and the right heart By passing the pulmonary capillary

by Schwartz, an incidence of 6.2 per cent was obtained in approximately 1[illegible],000 hogs fed on raw garbage, an incidence of 0.8 per cent in approximately [illegible],000 "grain fed" hogs and an incidence of 0.4 per cent in approximately 2,800 hogs fed on cooked garbage. In studies made in California, in which the hogs examined were traced back to the farm and the type of feed ascertained, Kerr found infection in 6.4 per cent of 1,701 hogs fed on raw garbage, in 0.6 per cent of 1,109 hogs fed on grain plus kitchen scraps, and in 0.5 per cent of 136 hogs fed exclusively on grain.

Certain types of pork products such as those customarily eaten without cooking by the consumer are very potent sources of trichinosis unless such products are adequately processed for the destruction of trichinae. These products include frankfurters, salami, mettwurst, cervelat, capacola, and the like. In the United States the Federal meat inspection regulations require the processing of these products before shipment in interstate commerce. That this processing is adequate is shown by the very convincing data presented by Schwartz, who found no viable trichinae in several thousand samples of such products.

A relatively high incidence of the parasite has been found in persons coming to necropsy in the United States. Wright, Kerr, and Jacobs gave figures on the National Institute of Health survey, which indicated an incidence of 15.9 per cent in 5,222 individuals autopsied in 168 hospitals in 37 states, the District of Columbia, and Puerto Rico. Omitting certain special series of examinations in which the findings were nil or practically nil, they found that the representative cases totaled 4,976, of which 831, or 16.7 per cent, were positive. In addition to the National Institute of Health studies, other investigators have reported in the United States a total of 5,88[illegible] examinations, of which 817, or 13.9 per cent, were positive for the parasite. This percentage includes no correction figures for inadequacies of the method of examination used in many of the surveys.

GEOGRAPHICAL DISTRIBUTION

Trichinosis has occurred in many parts of the world including Africa, Asia, South America, and the Caribbean area. In continental Europe Germany has long been an endemic center for the disease. Outbreaks have been reported in other European countries. A recent outbreak in Syria involved 500 cases. In England trichinosis was a rare disease until 1941, when several hundred cases occurred. Recent outbreaks have also been reported from Wales.

PATHOLOGY

Other than the tissue reaction in voluntary muscles and some other organs due to the encystment or arrestment of larvae, anatomic changes encountered in individuals succumbing to trichinosis are not peculiar to that disease alone.

An acute catarrhal enteritis is usually most marked in the duodenum and jejunum. There may be congestion and hyperemia of the mucosa with petechial hemorrhages and ecchymoses. The stomach may also show small hemorrhagic

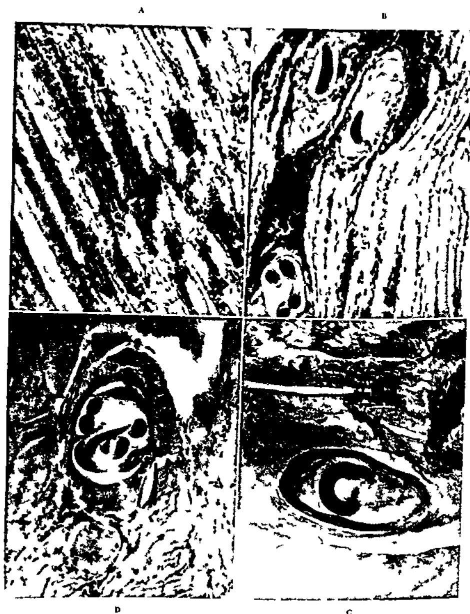


FIG 107 Trichinosis A Early lesion in experimentally infected animal showing young larvae lying straight in muscles B Cellular reaction in the surrounding tissues C Encystment partially complete less reaction D Calcified cyst

SYMPTOMATOLOGY

Many writers have described the symptoms of the disease on the basis of three general stages in the course of the illness these stages being the periods of invasion migration and encystation of the parasite However such a classification is more of academic than of practical value since these stages are not sharply defined A more accurate picture is presented if description is based on the severity of the disease There are three general types of cases The first group includes those with a severe fulminating infection and massive larval invasion of the tissues in which the patient exhibits the typical symptoms in an exaggerated form followed frequently by death in the second to third week of illness The second group includes moderately severe cases which run a stormy course but ultimately recover unless serious secondary complications ensue The third group comprises relatively mild infections in which the patient is only slightly ill

Mode of Onset The incubation period varies considerably depending on the amount of infected pork consumed the degree of cooking to which the meat has been subjected the number of trichina larvae per gram of tissue and probably also upon the general condition and the resistance of the host The onset may appear with almost dramatic suddenness in the form of severe gastro-intestinal symptoms simulating those of acute food poisoning These symptoms occur usually in those cases in which a very heavy infection has been acquired Nausea vomiting and diarrhea may follow in from twenty four to forty-eight hours after the ingestion of the infected pork In the absence of gastro intestinal symptoms most patients begin to show signs of illness from five to fourteen days after the ingestion of infected pork although in some instances the incubation period may be as long as three weeks In patients who have severe diarrhea at onset the generalized symptoms may not be as severe as in those in whom diarrhea has been absent

In the early stages the patient may also present symptoms suggestive of la grippe with a slight indisposition weakness inability to carry out his usual duties fatigue and possibly a slight fever Many of these patients are treated during the early stages as cases of mild influenza These symptoms may last for from seven to ten days During this period also there may be a maculo-papular eruption on the skin of the trunk and the extremities

Severe Infections These are characterized by marked toxemia The patient is prostrated the fever rises rapidly there is a swelling of the face and eyelids conjunctival edema may be present and in some cases this may be associated with hemorrhages extending from the external canthus to the pupil The temperature may rise to 40.5° C (105° F) or higher A rash may or may not be present and the patient may be delirious or in a stupor In severe cases the patient complains of excruciating pain The entire body may be so swollen that the skin seems to be tightly stretched over the tender musculature Adding to the discomfort is the severe pain which the patient experiences on respiration as a result of involvement of the diaphragm which is one of the

areas The mesenteric lymph glands are sometimes edematous and hemorrhagic. The liver frequently shows cloudy swelling and fatty changes The spleen is usually normal but may be slightly enlarged and show ecchymotic hemorrhages and infarction Cloudy swelling is often encountered in the epithelium of the renal tubules and infarcts have been noted in the kidneys in fatal cases of the disease

Lung changes may be extensive depending on the development of the disease Petechial hemorrhages may be present and intra alveolar hemorrhages may also occur Congestion may be present throughout In many cases pneumonia intervenes at about the fifth or sixth week of illness although sometimes earlier The pneumonia is of the lobular type and is probably due to secondary bacterial invasion following mechanical injury and lowering of the patient's resistance

When present cardiac changes are usually confined to the myocardium The larvae penetrate the muscle fibers and sometimes wander extensively throughout the heart although they do not encyst there Histologically the picture presents cloudy swelling fragmentation of the fibers extravasation of red cells and interstitial infiltration The predominant cells at the onset of the damage are lymphocytes with some mononuclears and a few eosinophils Later there is fibroblastic formation

Trichina larvae invade the central nervous system and may be found in the cerebrospinal fluid The spinal cord usually shows few lesions but larval invasion of the cerebrum produces a varying pathologic picture Most and Abeles summarized the findings of others and described the pathology they encountered in a fatal case with pronounced neurologic symptoms They agree with other observers in describing the picture as that resembling acute non suppurative meningo-encephalitis The lymphocytic granulomatous lesions were considered to be due to the presence of the larvae but those composed of microglial cells were probably of other etiology The perivascular infiltrations were considered to be late reactions to early acute hemorrhages

Profound pathologic changes occur in the voluntary muscles as a result of the invasion of the larvae The muscle fibers show cloudy swelling hydropic degeneration and areas of coagulation necrosis There is widespread focal interstitial infiltration characterized in the acute stage by the presence of numerous lymphocytes and polymorphonuclear leukocytes with some monocytes Eosinophils are usually not numerous Later the larvae may be surrounded by a clear undifferentiated pink staining hyaline like substance Fibroblastic infiltration later takes place and necrotic cellular elements are removed by macrophages Occasionally giant cells are seen in the invaded areas

The question of the toxic origin of some of the symptoms and lesions produced in trichinosis was studied in detail by Flury who believed that the twofold toxic injury to the body results through the accumulation of metabolic products of the parasite on the one hand and on the decomposition products of the damaged musculature on the other hand

only slightly incapacitated in fact some may even continue their normal routine In more severe cases the average duration is about three weeks Most of the patients have fever leukocytosis and muscle pains for that length of time Then the temperature begins to decline gradually taking about one week to reach normal During this period the patient is more comfortable the muscle pains generally subside the edema of the face disappears and by the end of the fourth week the patient is well along the road to recovery These changes occur regardless of the mode of therapy

In those patients who are desperately ill the period of disability is much longer and it may be a full month before the fever and other symptoms begin to subside In the fulminating type of case fatalities may occur in the first week Death may be associated with uremia coma cardiac failure and overwhelming toxemia Fortunately this type of case is relatively rare

The Chronic Phase After the patient has passed through the acute stage convalescence usually begins As a rule it is not possible to speak of a so called chronic phase of trichinosis in so far as clinical symptoms are concerned It is true that during convalescence the larvae are encysting and that the period of convalescence may be prolonged for two or three months depending on the severity of the infection and the response of the individual Many patients who have gone through an acute episode with high fever severe facial edema and marked muscle pains are able to return to work within two weeks after the fever has subsided These individuals have a certain amount of muscle pain especially upon motion

From a careful study of 70 patients who suffered from an acute attack of trichinosis Bercovitz found that 52 or 74 3 per cent had no residual symptoms between one month and one year following recovery Nine patients or 12 9 per cent had symptoms which lasted for varying periods of time but not longer than one year In two cases or 9 per cent it was questionable whether any symptoms were present In none of these cases did the symptoms persist for more than a year and in no case was there anything resembling a permanent disability

COMPLICATIONS AND SEQUELAE

The main complications of trichinosis are those related (1) to the presence of larvae of *T spiralis* within the body of the patient and (2) those which result from the lowered resistance of the individual to this infection The migration of larvae through the myocardium may produce evidences of acute inflammatory change The myocardial damage is indicated by electrocardiographic changes dependent edema râles at the bases of the lungs with evidences of passive congestion and shortness of breath If the invasion is heavy cardiac failure may occur during this period and is preceded by a rapid pulse and fall in blood pressure Recovery from the myocardial damage is usually relatively slow As a rule the electrocardiographic tracings indicate a return to normal in about three months

Involvement of the central nervous system may give rise to many different

muscles most heavily invaded It is during this period that various neurologic symptoms may develop The symptoms resemble almost any of those associated with acute conditions involving the central nervous system A very common picture is that resembling meningo-encephalitis or simple meningitis During this period symptoms of heart failure may appear Severe cardiac damage may result from the presence of the larvae in the heart muscle and in such cases definite electrocardiographic changes are demonstrable

In severe cases patients may continue to be acutely ill for three weeks or longer It is almost impossible to make the patient comfortable even with the administration of large doses of morphine In some instances the patients suffer from inability to swallow and cannot speak because of the edema resulting from the invasion of the muscles of the larynx Patients with severe involvement may die during this stage In those who survive as a rule by the twenty first day the temperature begins to subside by lysis about a degree in every twenty four hours so that by the end of the fourth week the temperature has reached normal

Moderate Cases Persons with moderate infections may show the same chain of symptoms as those encountered in severe fulminating cases but these symptoms are less severe Ocular involvement is usually present and frequently there is suborbital edema Generalized muscle pain is not so severe and it may tend to be more localized in isolated groups of muscles The temperature usually does not reach the same height and may resolve more quickly Cardiac symptoms are frequently encountered in these cases but electrocardiographic changes are not so pronounced and the cardiac involvement runs a milder course In most of the moderate infections neurologic symptoms are either not encountered or are very mild in nature The course of the moderate infections is usually shorter than in the severe cases and general prostration encountered in the latter is usually absent in the more moderate invasions

Mild Cases Not all patients with trichinosis present the picture of the severe or moderately severe forms The large majority start rather gradually and complain mainly of mild muscular pain which may or may not be so severe as to cause the individual to discontinue his work and force him to bed In most instances however the muscular discomfort leads the patient to consult his physician Swelling of the face and especially edema of the eyelids may be the symptoms which first attract the patient s attention Fever of varying degree is usually present and leukocytosis may be only moderate but with a distinct eosinophilia In the past many of these patients have been treated as cases of influenza which fail to respond to the usual home remedies or methods of the family physician As a result of the interest aroused by the work of the United States Public Health Service National Institute of Health physicians are becoming more conscious of the possibility of trichinosis in patients with relatively mild symptoms of this sort

Duration of Acute Phase The acute phase of the disease lasts from two to three days in very mild cases and to three or four weeks in the more severely infected individuals In many lightly infected cases the patients are

rise in the leukocyte count and occasionally leukopenia is present Most cases show some eosinophilia although persons suffering from concomitant bacterial or virus infections and those with an overwhelming invasion of trichinae may not show any change in the differential picture The eosinophilia may rise as high as 80 per cent but there is no definite correlation between the degree of infection and the eosinophil count Eosinophilia usually appears on the seventh or eighth day after infection although it may not become evident before the third week The percentage usually progresses rapidly to a peak but considerable variation may take place during the course of illness In severe cases a rapid drop may occur just before fatal termination

Intradermal and Serologic Tests Antigen for these tests is prepared from dried powdered trichina larvae Intradermal antigen is available commercially When carried out with proper dilutions of the antigen the tests are species specific and will seldom give positive reactions in the presence of other worm parasites

The intradermal test is carried out by injection with a 26 gauge ½ inch needle of 0 01 to 0 1 cc of a 1 10 000 dilution of the antigen into the skin of the forearm after suitable preparation of the site A control injection in the same arm is made with the diluent used in the antigen A positive reaction is of the immediate type and appears usually within fifteen to twenty minutes In rare cases there may be a delayed reaction which does not reach its height before twenty four hours When 0 01 cc of the material is used it is usually considered that the formation of a wheal with a diameter larger by 3 mm or more than that of the control wheal with or without pseudopodia represents a positive reaction The wheal is usually surrounded by a zone of erythema but the extent of the erythema is not as important from the standpoint of diagnosis as are the size of the wheal and the presence of pseudopodia The intradermal test is not usually positive until after the second week of infection

Precipitin Test Precipitin tests are carried out usually with antigen dilutions of 1 80 to 1 1 280 Phenol preserved antigen may give false positives Only clear non chylous non hemolyzed serum should be employed The precipitin test does not usually become positive until the beginning of the third week after infection The complement fixation test is used also but the precipitin test is simpler and in our experience has been somewhat more accurate

In evaluating these tests the clinician should take due cognizance of the fact that about one of every six persons examined at necropsy has a trichina infection it is possible that non-clinical infections may lead at times to positive reactions Furthermore persons who have recovered from trichinosis may continue to show positive reactions tissue sensitivity may persist for several years and reactions to the precipitin test may be encountered for as long as two years after recovery Since non specific reactions may occur infrequently too much reliance should not be placed on these tests but rather the results of the tests should be given due consideration in connection with the clinical syndrome the differential blood picture the history of the case and other factors

and often bizarre clinical pictures As a rule symptoms of central nervous system involvement appear early in the course of the disease and may even be some of the first symptoms observed The clinical picture may resemble encephalitis encephalomeningitis tuberculous meningitis poliomyelitis cerebral hemorrhage with local areas of paralysis and focal symptoms such as speech defects and symptoms involving the eighth nerve There may be coma or delirium restlessness muscular twitchings tonic or clonic spasms and it may be almost impossible to make an early diagnosis of trichinosis unless there is a very definite history of the consumption of pork products that have been improperly prepared As a rule these patients are desperately ill for a month or more although recovery is slow it is usually complete with no residual symptoms

Pneumonia is one of the commonest and most serious of the sequelae encountered As a rule it occurs from the third to the fifth week when the patient begins to show improvement and the attendants or the patient himself is a little less careful regarding exposures and chilling After the patient has begun to improve a sudden rise in the temperature curve with an increased leukocytosis *should serve as a warning of possible pulmonary* involvement The differential blood count may show a rise in neutrophils and a reduction in eosinophils After the acute condition has disappeared there is a shift again back to the original condition with the high eosinophilic blood count

So called neuritis arthritis and other somatic manifestations with pain stiffness and soreness of the muscles with or without limitation of motion may occur in almost any case of trichinosis These can hardly be considered as true sequelae or complications but in some instances they persist for varying lengths of time

DIAGNOSIS

A history of ingestion of uncooked or undercooked pork or pork products may often furnish a clue but the incubation period of the disease is so variable that the patient may not associate his illness with the consumption of pork For this reason sporadic cases are sometimes overlooked whereas epidemics involving a single source of food are more easily detected

Trichinosis must practically always be considered as a possible diagnosis in any acute systemic disturbance A differential blood count is indicated in acute illnesses *involving fever muscle pains and suborbital edema with or without* gastro intestinal symptoms The presence of eosinophilia under these conditions is strong presumptive evidence for a diagnosis of trichinosis More than one count is indicated in these cases since eosinophilia does not always appear early in the course of the disease Clinical observations should be supplemented by laboratory procedures intradermal and precipitin tests and if possible by biopsy

LABORATORY DIAGNOSIS

Blood Picture In most cases there is definite leukocytosis with the number of white cells ranging from 10 000 to 0 000 However not all cases show a

pathognomonic but are similar to those of many other conditions The gastrointestinal symptoms have been confused with those of typhoid fever food poisoning intestinal influenza colitis and appendicitis Manifestations caused by the presence of the larvae in the circulating blood and the voluntary muscles have been mistaken for conditions such as arthritis rheumatism upper respiratory infection laryngitis conjunctivitis influenza intercostal neuritis measles endemic typhus frontal sinusitis asthma pleurisy pneumonia and others The cardiac involvement may lead to a diagnosis of myocarditis or endocarditis Neurologic symptoms have been considered as indicating chorea encephalitis meningitis or poliomyelitis Actually of course some of these conditions may be present in individuals suffering from trichinosis and it is the difficult task of the clinician to determine their etiology

PROGNOSIS

The outlook for the immediate recovery of the patient depends on the degree of infection and his resistance If the patient appears to have a very severe invasion the prognosis must of necessity be guarded for a period of about three weeks In severe fulminating cases the prognosis is manifestly poor but in the moderately severe cases it is quite good After a patient has passed through the acute stages of the disease the ultimate prognosis is excellent

TREATMENT

There is no specific treatment for trichinosis since there is no known drug which will either remove the adult worms from the intestinal tract or destroy the larvae in the blood stream or voluntary muscles The general treatment of the disease in its acute phases is the same as that which is used in the general treatment of any acute condition The oral or parenteral use of chemotherapeutic agents such as arsenic compounds thymol hexylresorcinol the various sulfonamide drugs and so forth not only is of no value but is definitely contraindicated Any drug which is unnecessarily employed during the course of the disease is merely an added burden to the system consequently all such drugs should be avoided

Absolute rest in bed with adequate sedation is one of the most important procedures Sedatives must be freely administered in order to relieve the intense pain Acetylsalicylic acid (aspirin) in doses of 5 to 10 grains every three or four hours may be administered either alone or with codeine grains 1 in order to afford relief of the severe muscular pain For this purpose such preparations as nembutal dalvinal sodium seconal sodium amytal or sodium luminal may be used also If the administration of these drugs by mouth fails to give the desired effect it may be necessary to resort to the use of morphine

Fluids should be administered freely and for this purpose the use of fruit juices in amounts of 2 quarts or more in twenty four hours is indicated If the patient is nauseated with or without vomiting intravenous infusions may be necessary to provide an adequate fluid intake For this purpose 5 per cent glucose in normal saline is preferred This may be given in amounts

Biopsy Success in finding the larvae in biopsied muscle depends greatly on the degree of infection the time after infection at which the biopsy is made and the method of examining the tissue In lightly infected cases opportunities for detecting the larvae are conditioned largely by chance since the gastrocnemius quadriceps femoris and deltoid the muscles commonly biopsied are not those which are most heavily infected Biopsies made before the twenty first day after infection will frequently be negative since in many cases larvae will not have reached the muscles in sufficient concentration to be easily detected It is advisable to examine press preparations of muscle between heavy plate glass slides rather than to depend on sectioning the material The entire amount of muscle should then be digested in artificial gastric juice and the sediment examined for larvae Even with these methods we have found larvae in only 26 of 48 cases consequently a negative biopsy should not rule out a diagnosis of trichinosis

Examination for Larvae Examination of the blood spinal fluid and feces for trichina larvae is frequently made in cases of trichinosis but is not a reliable diagnostic procedure Isolation of larvae from these sources is accomplished in only a relatively small percentage of cases There is more hope of success in heavily infected cases but even in such cases the findings are not consistent

Cerebrospinal Fluid The fluid is usually clear colorless and under normal pressure Usually the cell count is within normal limits although high counts have been reported The sugar sodium chloride and total protein as well as albumin and globulin are usually within the normal range The colloidal gold test is usually negative

Urine Most cases have some albuminuria Casts have been reported but are probably due to some concomitant condition

Blood Chemistry In uncomplicated cases blood chemistry values are usually within normal limits Hanes found hypoproteinemia in one case and others are known to us In these cases the albumin is usually much lower than the globulin fraction Blood sugar values are nearly always within normal limits although Pierce and his associates found that low normals were averaged in their 44 cases They found also that non protein nitrogen approached the higher normal limits and early in the course of the disease noted a high blood phosphorus and a slightly low calcium Cholesterol and chlorides were usually normal Kaufman suggested that a lowered CO combining power might be expected but evidence does not indicate that the values are much altered It appears probable that these relatively slight blood chemistry deviations are due more to decreased food intake than to any specific effect of the disease

Information about the blood sedimentation rate is meager but indicates that the rate may be accelerated particularly in the second or third week of illness

DIFFERENTIAL DIAGNOSIS

Trichinosis has been confused with an astounding number of other diseases but this is not surprising in view of the fact that the symptoms are not

State or local inspection equivalent to Federal inspection the protection provided by the latter is limited

From a public health standpoint the logical approach to the problem of prevention lies in the control of the feeding of raw garbage to swine since the hog that is maintained on this type of food is on the average most frequently and most heavily infected The adequate cooking of garbage before its consumption by swine would eliminate much of the trichinous pork going on the market

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of 2 000 cc in divided doses over a period of twenty four hours (1 000 cc morning and evening) The glucose and saline should flow in very slowly not more than 30 drops a minute This therapy should be continued until the patient is able to take adequate fluids by mouth

Transfusions of whole blood or plasma may be given if the patient is acutely ill These may be administered in amounts of 500 cc every three or four days if necessary or until the patient is able to take adequate nourishment In this type of patient it is advisable to begin transfusions early and not wait until he is moribund

Preliminary purgation with Epsom salts is recommended in order to empty the bowel with the bare possibility that some of the adult worms may be swept out Due caution should be used not to dehydrate the patient

Fluids should be administered by injections only until the patient is able to retain more solid food There is no indication for starving a patient during an acute attack of trichinosis The diet should be well balanced Most patients feel better when given plenty of proteins especially in the form of meat in addition to the carbohydrate intake Fruits and vegetables are also indicated as well as are foods that are known to be high in vitamin content

The use of iron in some form either by mouth or parenteral injection is indicated The administration of some of the vitamin preparations is acceptable also Where there are severe symptoms of neuritis thiamin hydrochloride should be given The value of various calcium injections and of the use of cod liver oil and vitamin D preparations has not been demonstrated

Good nursing is of the greatest importance This includes not only the routine matter of bathing but such comforts as can be given to a patient who is acutely ill and whose muscles are so exquisitely tender that it is almost impossible for him to be at rest in any position A cradle to keep the bed covers off the patient s body and adequate protection from drafts and chilling are of greatest importance

PROPHYLAXIS

Trichina larvae are killed on exposure to a temperature of 55 C (131 F) although the Federal meat inspection regulations require processing at 137 F in order to provide a margin of safety The thorough cooking of pork therefore should render the meat safe for consumption without danger of contracting trichinosis However the individual does not always have control over the preparation of the food which he consumes For this reason and others control of the disease should go beyond individual prophylaxis While some European countries require the microscopic inspection of pork in the United States practically the only control measure operative in the past has been that part of the Federal meat inspection regulations relating to the processing for the destruction of trichinae of pork products customarily eaten without cooking by the consumer While these regulations insure nearly absolute safety from this standpoint only about 70 per cent of the pork marketed in the United States is slaughtered under Federal inspection Since there is very little

State or local inspection equivalent to Federal inspection the protection provided by the latter is limited

From a public health standpoint the logical approach to the problem of prevention lies in the control of the feeding of raw garbage to swine since the hog that is maintained on this type of food is on the average most frequently and most heavily infected The adequate cooking of garbage before its consumption by swine would eliminate much of the trichinous pork going on the market

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CHAPTER LXIII

THE NEMATODES (ROUNDWORMS) III FILARIAE AND GUINEA WORMS

J ALLEN SCOTT AND Z T BERCOVITZ

THE FILARIAE FORM A DISTINCT GROUP OF WORMS THAT are transmitted through the bites of insects For convenience the guinea worm is often classified with them Although some species of filariae in animals are found in the heart those of man commonly inhabit the lymphatic system or the connective tissues These worms do not lay their eggs the embryos develop rapidly in the uterus and leave it as motile larvae known as microfilariae When these larvae are taken up from the blood or tissues by some species of insect during the act of biting they undergo metamorphosis in the insect and localize in the mouth parts where they are ready to infect the next person bitten They do not however undergo any multiplication in the insect host

The guinea worm is only a distant relative of the filariae but it is similar to some of them in respect to its habitat in the subcutaneous tissues This worm spends only the latter portion of its life there however for it has evolved a unique means of getting the embryos out of the body through a lesion in the skin in addition to a marvelous mechanism for ensuring that some at least will stand a chance of falling into water containing *Cyclops* the intermediate hosts

FILARIASIS

Wuchereria bancrofti and Wuchereria malayi

Two species of filarial worms are known to cause lymphangitis and elephantiasis The most common and best known of these is Bancroft s filaria now known officially as *Wuchereria bancrofti* The adults of this species are slender white worms which live in the lymph vessels and glands and are thus seen only at autopsy They are not easily distinguished from other related species consequently when identification is desired they should be preserved for examination by specialists The males are about 40 by 0 1 mm and the

females usually measure about 90 by 2 5 mm The adults of W malayi have only recently been found and differ from those of W bancrofti in minor anatomic details (Bonne 1941)

LIFE CYCLE AND METHOD OF TRANSMISSION

While still in the uterus of the adult worm the embryos develop rapidly in the eggs and escape into the lymph stream as active elongated larvae known as microfilariae From the lymphatics they pass into the blood stream In most parts of the world the microfilariae of W bancrofti (Plate XX) appear in the peripheral circulation at night only especially between the hours of 10 P M and 2 A M In the Philippine Islands and other Pacific islands they have no such periodicity but are apt to be found in the blood at any hour W malayi (Plate XX) also has a nocturnal periodicity but the larvae do not entirely disappear from the blood during the day Observers have reached no agreement as to the causes and mechanism of periodicity (Hinman 1937 Lane 1937)

The infection is transmitted from one person to another by certain mosquitoes The most common vector of W bancrofti is *Culex quinquefasciatus* (*C fatigans*) but many other species belonging to various genera including *Aedes* and *Anopheles* have been incriminated W malayi is principally transmitted by species of the genus *Mansonioides* When the microfilariae enter the stomach of the mosquito most of them penetrate the wall and invade the thoracic muscles Here they undergo extensive development during a period of from ten days to several weeks They then migrate to the tip of the proboscis sheath (Abe 1937 Yokogawa 1938 1939 b) When the mosquito again bites the larvae emerge through the thin wall of the sheath onto the skin and enter the puncture wound made by the proboscis Once in the skin they migrate to the lymph spaces where they mature

PATHOLOGY AND SYMPTOMATOLOGY

Many infected persons show no symptoms whatever and it seems likely that many infections never cause much reaction On the other hand the disease develops only after the infection has existed for some time and probably only as a result of repeated or massive infection The mechanism by which the characteristic elephantiasis is produced is still not clearly established but there is a growing opinion that the living worms produce little or no effect Dead worms may be solely responsible or else a secondary bacterial infection which frequently occurs may be a contributing cause (O Connor 1932 Drinker *et al* 1935) Once started the disease may or may not be progressive (Knott 1938) but in the later stages the prognosis is poor although the patient may live for years The early symptoms are urticaria fever and other acute manifestations These are associated with a lymphangitis which is usually located in the upper extremities in the case of W malayi and in the lower in the case of W bancrofti The subsequent developments are similar for the two species except for the differing location but they have been more extensively studied in the case of

W bancrofti The lymphangitis may be followed soon or after a long interval by lymph varix or other symptoms of lymph blockage Naturally the symptoms vary according to the location of the blockage and may involve the organs of the abdomen any of the lymph glands the scrotum testes epididymis vagina and other parts of the body Chyluria and chylous diarrhea have been reported The elephantiasis may or may not develop in the same locations it is most common on the scrotum and lower limbs The elephantoid tissues become covered by a rough coarse hypertrophied and fibrous skin Microfilariae often cannot be found in the blood once the elephantiasis has begun probably because the worms have been blocked off or are dead

DIAGNOSIS

The microfilariae can best be found in thick blood films as prepared for the diagnosis of malaria (page 169) In most parts of the world the blood should be taken between the hours of 10 P M and 2 A M Giemsa stain is the most satisfactory for rapid diagnosis but for more careful study the slides should be dehemoglobinized and stained with haemotoxylin with or without a counterstain

The microfilariae of these two species must be differentiated (Plate XX) from those of *Loa loa Acanthocheilonema perstans* and *Mansonella ozardi* (Table IX) all of which occur in the blood To a certain extent the geographical region in which the patient is likely to have become infected will indicate which species may be present Three species of microfilariae found in human blood are covered with thin sheaths which are usually best seen where they extend beyond the body at one or both ends Of these *W malayi* (length 160 to 230 microns) may be distinguished from the other two by its sharply pointed tail which contains only two nuclei one at the tip and one slightly forward On the other hand the tail of *Loa loa* (length 2 5 to 300 microns) is often bent and contains nuclei to the tip while the tip of the tail of *W bancrofti* (length 25 to 300 microns) contains no nuclei and is usually straight The two latter species can be further differentiated by their appearance in dried blood films *W bancrofti* lying in graceful curves while *Loa loa* is usually broken into short curves and twists presenting an ungraceful almost angular appearance When a drop of fresh blood is mixed with a drop of methylene blue stain in dilution 1 5 000 *W bancrofti* does not take up the stain for some time while *Loa loa* begins to stain within about ten minutes (Sharp 1923) The two other common species do not have sheaths They can be distinguished in that *A perstans* (length 100 to 200 microns) has a blunt tail with nuclei extending to the tip while *M ozzardi* has a sharp tail with no nuclei at the tip Both stain with methylene blue Other characters for differentiating these and the rarer species can be used after a more elaborate staining procedure

The primary febrile attack in filariasis must be differentiated from that of malaria and other fevers Sometimes the early effects of lymph blockage may appear to be due to other conditions Varicose groin glands can be differentiated from hernias which they resemble in that these glands convey little or

no impulse on coughing disappear slowly when the patient lies down and reappear on standing in spite of pressure on the inguinal openings The fact that other causes of elephantiasis exist should not be overlooked but as already mentioned the microfilariae may not be demonstrable after the elephantiasis has become established Roentgenograms may show characteristic tiny spots where the worms have become calcified and may be useful in diagnosis (O Connor Golden and Auchincloss 1930) Intradermal reactions are only group specific and are positive in about 80 per cent of the cases (Fairley 1931 Taliaferro and Hoffman 1930)

TREATMENT

There is no specific drug known for the treatment of filarial infection The sulfonamide drugs have been useful in some cases complicated with sepsis The most helpful procedure in early non inflammatory elephantiasis of the limbs has been pressure bandaging some walking being required to prevent cyanosis (Knott 1938) Operative intervention to relieve the lymph blockage is not advised The fibrotic tissues of elephantiasis may be surgically removed This procedure is most successful in the case of scrotal elephantiasis but the relief in other cases is only temporary (Auchincloss 1920)

EPIDEMIOLOGY

The geographical distribution of *W bancrofti* is world wide in the tropical belt and it occurs as well in many parts of the subtropics In general it can be said to be more common along the coasts than in the interior of the countries with varied topography Its distribution is spotted not affecting all parts of most countries and in many places being distinctly localized Prevalence rates for various countries do not apply to the entire country therefore In most places relatively few people are infected but in a number of places such as Samoa parts of India China Fiji and the East Indies the prevalance may be as high as 80 per cent of the population The disease develops so long after infection has taken place that the symptoms are most common in people of middle age or at least past their childhood The rate of infection in mosquitoes has usually been found to be much lower than the incidence among human beings of the same localities Infection with *W malayi* is confined to the Far East as far as is yet known corresponding to the distribution of the principal intermediate hosts which belong to the genus *Mansonia* It also differs from *W bancrofti* in that the prevalence is higher in persons with clinical symptoms while in the cases of *W bancrofti* the reverse is true probably because the worms have been blocked off or are dead by the time advanced symptoms are noticeable

Loa Loa

Although *Loa loa* is usually called the eye worm it only occasionally gets into the eye Ordinarily it inhabits the subcutaneous connective tissues The cases reported from the Western Hemisphere were probably contracted in

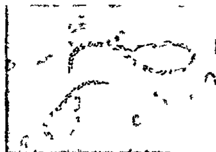
TABLE IX

DIFFERENTIAL DIAGNOSIS OF MICROFILARIAE

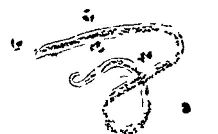
I NAME	LOCATION
Wuchereria bancrofti	Night blood urine (chyluria) hydrocele fluid
Microfilaria malayi	Night blood but occurs during the day in small numbers
Loa loa	Day blood (9 A M to 2 P M) Adult migrates around body especially to eye
Acanthocheilonema perstans	Day and night blood (non periodic)
Mansonella ozzardi	Day and night blood (non periodic)
Onchocerca volvulus	Skin subcutaneous nodules hydrocele fluid lymphatic glands Puncture of nodule may yield egg with microfilaria
Microfilaria streptocerca	Skin
II SHEATHED MICROFILARIAE FOUND IN BLOOD STREAM	
W bancrofti	Body graceful curves tail tapers to point nuclei do not reach tip of tail
M malayi	Tail contains 2 nuclei (1 at tip and 1 slightly forward) Swellings at levels of these nuclei
Loa loa	Body angulated tail tapers gradually nuclei continuous with those of body reach tip of tail
III UNSHEATHED MICROFILARIAE FOUND IN BLOOD STREAM (No periodicity occur in blood stream both day and night)	
A perstans	Blunt tail nuclei continuous to tip
M ozzardi	Pointed tail nuclei do not reach tip
IV UNSHEATHED MICROFILARIAE NOT FOUND IN BLOOD STREAM	
O volvulus	Nuclei do not reach tip of tail
M streptocerca	Nuclei reach tip of tail



1 Loa loa



Ac thoche lon a pe stans



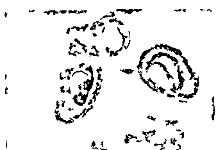
3 Wuche r bancrofti



4 M ofil malayi



5 M o ll o a d



6 Onchoce ca v l ul

PLATE XX

The Microfilariae

Original photomicrograph (retouched) Loa loa (× 7,6) from teaching slide by Liverpool School of Tropical Medicine loaned by Puerto Rico School of Tropical Medicine W bancrofti (× 7,6) (Z T B) Puerto Rico Survey M malayi (× 9,0) specimen by courtesy of Dr W W Cort Other specimens are from preparations by the late F W O'Connor

Central or West Africa where the infection is highly endemic in some places affecting 90 per cent of the population

The adult males are about 30 to 35 mm in length and about 4 mm in diameter at the anterior end tapering posteriorly Similar measurements for the females are 50 to 70 by 0 5 mm The larvae have been described in the discussion of *W bancrofti* (Plate XX Table IX)

LIFE CYCLE

The microfilariae leave the females in the connective tissues and are found in the peripheral blood between the hours of 9 A M and 2 P M The infection is transmitted from person to person by deer flies of the genus *Chrysops* (Leiper 1913 Connal and Connal 1921) The microfilariae ingested by the flies require a period of at least ten days to develop to the infective stage

PATHOLOGY AND SYMPTOMATOLOGY

Most of the time the worms move about in the passages that they have made in the subcutaneous connective tissues without inducing pathologic reaction or symptoms other than a slight irritation For the most part they are confined to the subcutaneous tissues of the head but they have occasionally been found in other parts of the body Occasionally these worms migrate across the eyeball beneath the conjunctiva causing considerable alarm but no serious results have been recorded Infected persons are also subjected to intermittent swellings under the skin commonly known as fugitive or Calabar swelling These painless lumps an inch or so in diameter last but a few days They may be caused by secretions which are given off by the worms when they become stuck in the tendon to aid in freeing themselves (Leiper) or they may be an allergic manifestation of some other character (Chandler Milliken and Schuhardt 1930) Recurrences may cause cystlike swellings of the tendons which may become painful and occasionally the worms will cause pain when passing near sensitive structures such as the urethra

DIAGNOSIS

The microfilariae can be identified in blood films taken during the morning by means of the characters mentioned in discussion of *W bancrofti* (Plate XX Table IX) The group specific intradermal tests are probably most sensitive for *Loa loa* The appearance of the worm under the conjunctiva often makes diagnosis possible

TREATMENT

No specific drug is known The worms can be removed from the conjunctiva with a hooked needle if the operator works with dexterity Whenever they can be accurately located in the subcutaneous tissues they can also be dissected from their channels there Heliobrom is suggested to control the urticarial dermatitis when this is present (Manson Bahr 1935)

EPIDEMIOLOGY AND PROPHYLAXIS

Little is known of the epidemiology of this disease The flies lay their eggs on waterplants The early larval stages are aquatic but the later larval stages live in mud near the water The adults are daytime shade biters common in wooded ravines and personal prophylaxis is based on this knowledge Little progress has been made in the control of the disease

Onchocerca volvulus

The worms causing onchocerciasis both in Central America and Africa belong to the species *Onchocerca volvulus* They are found in subcutaneous tumors and connective tissue but can seldom be removed intact The males are from 0 to 40 mm long and about 150 microns in diameter while the females are on an average about twice as thick and from 30 to 50 mm long

The microfilariae do not occur in the blood but live in the cutaneous tissue juices They are not sheathed vary from 150 to 400 microns in length and have no nuclei at the tip of the tail (Plate XX Table IX)

LIFE CYCLE AND METHOD OF TRANSMISSION

The microfilariae are taken up from the tissue of the skin somehow in the process of biting by certain species of flies of the genus *Simulium* which were shown by Blacklock (1926) to be the vectors

In the flies the larvae go through a period of development which requires at least six days They then locate in the proboscis sheath ready to emerge and penetrate the skin when the fly bites again

PATHOLOGY AND SYMPTOMATOLOGY

The most obvious pathologic effects of this infection are the subcutaneous tumors or nodules varying in size up to 5 or 6 cm These nodules may contain several adult worms or only one pair The microfilariae may be found in any fluid which the nodule contains or in the surrounding tissues The young nodules are inflammatory in character and somewhat granulomatous being composed of polymorphonuclear leukocytes eosinophils phagocytes and round cells They are not however richly vascularized like true granulomata of yaws or verruga peruana Later on more fibroblasts and endothelial cells are found in a more or less organized fibrinous exudate while the older nodules outside the inflammatory areas are composed of fibrous connective tissue or masses of collagen fibers (Strong 1934 Strong *et al* 1938) The nodules are slow growing and benign and may or may not be painful

Most persons in endemic areas have from one to six nodules but in a few districts where nearly every person is infected the average is much higher than this Occasionally a person may have 100 or more In Central America the nodules are chiefly on the head but in most of Africa they are only rarely so situated commonly occurring on the trunk especially over the intercostal

spaces about the pelvis and over the joints of the long bones In a few intensely endemic areas of the Belgian Congo however the nodules are characteristically found on the head (Hissett 1933) The cause of these differences in location has not been determined although numerous explanations have been offered (Strong *et al* 1938)

In those regions where the nodules occur on the head involvement of the eyes is also common These lesions begin typically with inflammation of any of the various ocular tissues but especially with keratitis accompanied by extensive vascularization Sometimes the lesions may include retinochoroiditis leading to atrophy of the optic nerve In any case optic disturbances are common and partial or complete blindness frequently ensues

DIAGNOSIS

The microfilariae can often be obtained by drawing fluid from the center of the nodules If no liquid seems to be present sterile saline which can be injected and retrieved may contain larvae They can also be obtained from the skin by shaving off a thin paring with a sharp razor not going deep enough to draw blood Sometimes the larvae can be obtained from the skin of persons showing no nodules Apparently in such cases the nodules are located inside the ribs or other bones The microfilariae so obtained ordinarily appear as just described but if an adult female happens to be punctured with the needle immature larvae sometimes still in the egg shell may be found Eosinophilia occurs in this infection as in many helminth diseases

TREATMENT

The most satisfactory treatment is enucleation of the nodules Drugs can be injected into the center of the nodule in an attempt to kill the adult worms gentian violet and hexylresorcinol having been shown to be of some promise for this purpose (Strong 1937) Antimony preparations by vein or intramuscularly as for schistosomiasis apparently kill the microfilariae and perhaps inhibit the production of more for a time Injection of 0 1 per cent plasmochin solution is recommended to arrest the ocular symptoms by killing the microfilariae in the vicinity (Faust 1939)

EPIDEMIOLOGY

This infection is endemic on the southern or Pacific slopes of Guatemala and Mexico and in various parts of West Central and East Africa In Central America the flies breed at altitudes of 2 000 to 4 500 feet in swift streams flowing in the bottom of steep valleys on the sides of which coffee is grown It is especially in connection with the work in the coffee groves that the inhabitants frequent places where the flies bite In Africa the flies are found at altitudes below 1 000 feet and up to about 1 500 feet where they breed in wooded streams Here also agricultural pursuits may be a factor in bringing the people into fly infested areas but domestic tasks such as bathing or procuring water from the streams also play a part Wild and domestic animals are infected

with species of *Onchocerca* some of which are morphologically identical with the human parasites but there is no evidence that the reservoir hosts play any essential part in the epidemiology of the human disease

PROPHYLAXIS

No entirely satisfactory preventive or control measures have been developed against this infection The breeding areas are sharply circumscribed and personal prophylaxis therefore consists in avoiding these areas where the flies are biting freely Since the proportion of flies found to be infected is low except in a few regions the infection is usually acquired only by those who get many bites Systematic removal of all early nodules should be helpful in preventing the ocular disturbances and this procedure has been advocated as a means of protecting the general public as well (Strong 1937) Cutting brush might establish protection in some regions but where agricultural pursuits such as coffee raising are involved this type of control is impracticable Some methods for controlling the breeding of flies of this type have been successful experimentally but do not appear applicable on a large scale

Acanthocheilonema perstans and Mansonella ozzardi

These two *Filariae* have not been shown to produce symptoms and are only important from a medical point of view in that their microfilariae may be confused with those of the pathogenic species The differences are described (Plate XX Table IX) under the discussion of *W bancrofti* *Acanthocheilonema perstans* has been reported from various parts of Africa and South America *Mansonella ozzardi* is found in parts of South and Central America and the West Indies Both species are transmitted by sandflies of the genus *Culicoides* Other species of filariae have been described but are inadequately differentiated at the present time

THE GUINEA WORM (DRACUNCULUS MEDINENSIS)

The presence of the guinea worm is noticed only near the end of her life when she locates in the subcutaneous tissues and produces a blister on the skin These adult females may be as long as 1 0 cm but generally average somewhat under 1 meter in length and less than 1 5 cm in diameter The only male worms recovered from a human case measured 40 mm in length while those from experimental animals have been about half that length (Moorthy 1937) The larvae which are about 600 microns long have a blunt anterior end and a filamentous tail

LIFE CYCLE AND METHOD OF TRANSMISSION

The life history of the guinea worm was worked out in general outline by Fedtschenko in 1871 and details have been added by others most recently by Moorthy (1937 1938) Little is known about the development of the adult worms until the gravid female localizes under the skin about a year after infection has taken place The lesion is usually on the lower extremities and

begins with the formation of a vesicle or blister over the anterior end of the worm This blister soon ruptures and if the lesion then comes in contact with water the worm contracts and so produces a rupture of the body wall near the anterior end Through this opening a loop of the uterus prolapses and bursts releasing numerous larvae into the water At each contact with water at intervals of not less than an hour the process is repeated until the contents of the uterus are exhausted The worm may then emerge or be absorbed in situ The next step in the life cycle depends on the larvae being swallowed by certain species of water fleas of the genus *Cyclops* In these crustaceans the larvae penetrate the intestinal wall and localize in the body cavity where they undergo a metamorphosis which takes about ten days If the infected intermediate hosts are then swallowed by man in his drinking water the larvae can be freed in the intestinal tract They penetrate the tissues and probably continue developing in the deeper connective tissues and only become evident about a year later when the female seeks the body surface

PATHOLOGY AND SYMPTOMATOLOGY

The early symptoms of this infection appear shortly before the time of the appearance of the blister and may include itching and giant urticaria dyspnea and syncope nausea vomiting and diarrhea (Fairley 1924) When the blister bursts a few hours later the symptoms quickly subside The lesion through which the embryos escape remains open for a month or more under ordinary conditions but if maintained in an aseptic state and hourly applications of water are used to hasten the ejection of embryos the course can often be completed in a little more than a week The serious pathologic conditions usually seen are those associated with secondary bacterial invasion of the opening and at times along the entire length of the worm Naturally there are numerous complications Among them arthritis is common and death is usually the result of septicemia In the endemic areas large numbers of people are incapacitated for months at a time

DIAGNOSIS

The symptoms are followed so soon by ulcer formation that there is usually little doubt as to the cause Positive confirmation can be obtained by finding the typical embryos in the exudate from the lesion

TREATMENT

Adrenalin will control the early symptoms Care and treatment designed to prevent and control secondary bacterial infection of the lesion are important Healing can be hastened by removing the worm The time honored method for doing this is to douse the opening with water until the worm can be grasped then to wind it on a stick and slowly continue to wind it as the movements of the worm allow In the hands of ignorant practitioners this method often results in breaking the worm by pulling too fast while compresses containing septic material are often used on the opening In either case the matter is made worse

by the bacterial infection carried back into the channel Carried out with aseptic precautions however this method may often be successful but the worm should first be induced to discharge all her embryos by hourly applications of sterile water Fairley and Liston (19 4) recommend cutting out the worm in pieces by cutting through the skin at several points but care must be taken to avoid drawing the anterior end back through the tunnel

EPIDEMIOLOGY

Guinea worm infection occurs primarily in regions where rainfall is deficient and where water is stored under primitive conditions In these regions the distribution of the infection is not uniform but the reason for the absence of the infection from localities within the endemic area are still obscure The infection is most common in India and parts of tropical Africa but it also occurs in various regions of the Middle East and in a small area in Brazil Transmission is effected by the use for drinking purposes of water from ponds pools step wells and the like into which the people walk to fill their con tainers In the driest seasons of the year the water supply is reduced to such sources and consequently the greatest concentration of people is found here In such water supplies the greatest concentration of *Cyclops* also occurs

Since the life cycle requires about a year the infection shows a marked seasonal distribution Not all species of *Cyclops* will transmit the infection but some of the appropriate species appear to be present wherever human habits and climatic conditions provide suitable conditions In many countries animals have been found infected with various species of guinea worms some of which are indistinguishable from the human form No evidence exists however to indicate that they play any part in the epidemiology of the human disease

PROPHYLAXIS

Personal prophylaxis consists in drinking only filtered or boiled water Per manent control of the infection can be effected by rebuilding the sources of drinking water so that people cannot enter the water (Leiper 190, Moorthy 1932) Religious and other customs often make this difficult however and some success has followed temporary means of control The addition of lime to the water in proportions of 1 1000 has been helpful (Pradhan 1930 Davis 1931) Moorthy (193) has been able to control *Cyclops* by monthly applications of bleaching powder (perchloron 3 lbs to 100 000 gals) and copper sulphate (1 lb to 200 000 gal) Stocking the water with species of fish which eat *Cyclops* has also been successful (Moorthy and Sweet 1936)

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begins with the formation of a vesicle or blister over the anterior end of the worm This blister soon ruptures and if the lesion then comes in contact with water the worm contracts and so produces a rupture of the body wall near the anterior end Through this opening a loop of the uterus prolapses and bursts releasing numerous larvae into the water At each contact with water at intervals of not less than an hour the process is repeated until the contents of the uterus are exhausted The worm may then emerge or be absorbed in situ The next step in the life cycle depends on the larvae being swallowed by certain species of water fleas of the genus *Cyclops* In these crustaceans the larvae penetrate the intestinal wall and localize in the body cavity where they undergo a metamorphosis which takes about ten days If the infected intermediate hosts are then swallowed by man in his drinking water the larvae can be freed in the intestinal tract They penetrate the tissues and probably continue develop ing in the deeper connective tissues and only become evident about a year later when the female seeks the body surface

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diagnosis Even hookworm eggs appear in these preparations with great regularity but for these flotation is more delicate

FLOTATION

Several methods have been based on the principle of floating the eggs on a fluid of higher specific gravity than the eggs themselves The most commonly used solution is one of sodium chloride For optimum results the salt in excess should be dissolved in boiling water and the solution filtered after cooling Only in this way can the needed specific gravity of 1 200 be constantly attained Zinc sulphate solution of specific gravity 1 180 has recently been introduced (Faust *et al* 1938) and appears to be as effective as the heavier salt solution (Otto Hewitt and Strahan 1941) It is said to produce less osmotic effect but this is a greater advantage in protozoological diagnosis than in helminthological techniques

The procedures and apparatus for various flotation methods vary greatly but the following are probably the most widely used methods

Willis Salt Flotation

Various modifications of the method introduced by Willis (1921) have been widely used in surveys

The procedure calls for the mixture of about 1 gm of feces with an equal amount of saturated sodium chloride solution in a shallow cylinder or salt cellar about 2 5 cm in diameter While constantly mixing with a glass rod or wood applicator the technician adds gradually more and more of the salt solution until the fluid level is just at the edge of the container but does not form a meniscus above the edge Care must be taken not to allow the fluid to flow over the edge of the container lest the eggs which are floating be lost A clean grease free slide is carefully superimposed on the edges of the container in contact with the fluid and allowed to remain there for about ten or fifteen minutes During this time the ova which are free in the mixture will gravitate to the under surface of the slide The slide is removed vertically and is rapidly turned over so that a collection of fluid is on its upper surface These preparations are usually examined uncovered but a coverslip may be placed gently on the fluid If the coverslip is pressed down on the slide too firmly the egg shells will be broken and it will be impossible to make out the distinguishing characteristics of the ova For the microscopic examination it is important to adjust the substage condenser so that the light focuses upon the fluid being examined It is also important to use a mechanical stage to insure systematic and complete examination of the slide The low power ocular is used first to locate the eggs and the final identification is made with a higher power if necessary

In the clinical laboratory where specimens are examined in small numbers and are received in various types of containers a convenient modification of this technique is to stir the specimen in a small paper cup in a little salt solution dilute further and stir again then pour through a gauze strainer into a test

CHAPTER LXIV

CLINICAL LABORATORY DIAGNOSIS OF HELMINTHS

J ALLEN SCOTT AND Z T BERCOVITZ

ONLY A FEW OF THE MANY METHODS DEVISED FOR THE finding of helminth eggs in feces have come into common use Even these few are based on still fewer physical principles

SMEAR

The simple smear of feces on a slide mixed with a little physiologic saline and examined either with or without a coverglass provides the easiest means of diagnosis and reveals most of the positive specimens The most common mistake made by the uninitiated is to make the smear too thick Smears for the diagnosis of *Schistosoma* spp should be made from any blood or mucus seen on the surface of the stool

SEDIMENTATION

Many methods have been devised for the concentration of helminth eggs by means of sedimentation Usually the feces are comminuted in water and sometimes the coarser particles are strained out by passing the mixture through gauze or a wire screen of from 20 to 80 mesh A conical urine glass furnishes the best means of concentrating the sediment which may be removed from the bottom with a pipette and spread on a large slide within a ring made by a greased pencil Except for fragile eggs such as those of the hookworms these preparations as well as open smears may be dried and later examined after they have been remoistened with water or oil The eggs are then all in one plane and the liquid holds no floating debris Where egg counts are made the diluted material can be sedimented after counting so as to discover any types of eggs which were present in too small numbers to be found in the minute quantity counted Eggs of *Schistosoma* spp are most readily found by this method but some stools *flocculate and prevent the sedimentation of the eggs* Eggs of *Trichuris* and *Ascaris* are found more readily by this method than by flotation because they are heavy although both methods are adequate for

a group of people Their extension for clinical use is not completely satisfactory as the accuracy of the individual counts is not great because of a high random error However the methods can be very useful to the clinician to indicate whether many or few worms are likely to be present Repeated examinations will rapidly eliminate the errors in cases deserving special study

The most widely used egg counting method is the modification of Stoll's method suggested by Stoll and Hausheer (19 6) Other modifications have been used by various persons but have not proved to be so convenient in most laboratories This method calls for special flasks and pipettes (Scott 1932) but in the clinical laboratory where high accuracy is not needed these can be improvised The flask is filled to the 56 cc mark with N/10 NaOH solution and feces are added to the 60 cc mark Glass beads are added and a preliminary shaking is given The following day the flask is shaken until all particles are broken up 0 075 cc is removed a 2 by 30 mm coverglass added and with a mechanical stage the whole is systemically examined and all eggs counted The results multiplied by 200 give the estimated number of eggs per cubic centimeter of stool

EXAMINATION OF URINE FOR HELMINTH EGGS

The only eggs commonly found in the urine are those of *Schistosoma haematobium* They are relatively heavy and can be sedimented out of the urine in a conical cup in half an hour or less Preparations made from the sediment can be dried on the slide and remoistened for examination a number of times if necessary without affecting the appearance of the egg shells

BLOOD EXAMINATIONS FOR MICROFILARIAE

The methods for making thick and thin films of blood for malaria diagnosis (page 169) serve equally well for diagnosis of filariasis

DIAGNOSIS OF MICROFILARIAE

1 Examination of fresh blood is made by placing 4 or 5 large drops of blood on a glass slide and smearing in a circle about 1 cm in diameter This should be examined wet with the low power objective for motile living larvae

2 Ten cubic centimeters of whole blood are mixed with 100 cc of 3 per cent acetic acid After dehemoglobinization is complete centrifuge at high speed for one hour Examine sediment for larvae

3 Five cubic centimeters of blood is allowed to clot in a glass tube The portion of serum adjacent to the blood clot is examined for microfilariae If none are found the entire tube should be centrifuged at about 1 800 R P M for one or two minutes and the sediment examined for microfilariae

STAIN TECHNIQUE FOR MICROFILARIAE

1 Place thick drops of blood or sediment from centrifuge on glass slide
2 Allow to dry
3 Dehemoglobinize blood on slide in tap water

tube After twenty minutes the surface of the liquid is removed to a slide with a wire loop or the open end of a smaller tube

Direct Centrifugal Flotation (D C F)

This method which was introduced by Lane (192[illegible]) requires a special centrifuge or one adapted to the purpose One gram of feces is added to some water *in a special tube with a ground top Shot is added the tube corked* and shaken to mix well The tube is then centrifuged for one minute at 1 000 R P M The water is poured off the sediment salt solution of specific gravity 1 [illegible]00 is added and the tube inverted carefully to mix without forming bubbles The tube is then placed in the centrifuge and filled level full with the salt solution A coverslip is laid on the ground top and is held in place by four prongs extending from the sides of the buckets After spinning at the same speed for a minute the centrifuge is allowed to stop without jarring the cover lifted briskly and placed on a slide for examination This method will reveal more light cases of worm infections with such light weight eggs as those of hookworm than any other method It is seldom that such extreme delicacy is needed however and the method has been little used except in experimental work

Zinc Sulphate Centrifugal Flotation

This technique is described in detail in the section on diagnosis of protozoal infections (page 32) As far as helminths are concerned the technique is essentially similar to the direct centrifugal flotation method and produces equally good results (Faust *et al* 1938) A special value of this method is that *protozoan cysts and helminth eggs can be found in the same preparation*

Modified Zinc Sulphate Flotation Method

A modification that requires less apparatus and time has been described by Otto and his associates (1941) and it appears to be equally as good for helminthological purposes at least In this method zinc sulphate specific gravity 1 180 is used instead of brine as in the Willis salt flotation method The rest of the technique is the same as that outlined for the preceding method Eggs of *Schistosoma mansoni* and probably others of high specific gravity do not appear with regularity on these preparations Theoretically a higher concentration of the solution should be used but in preliminary experiments by Scott eggs of *S mansoni* were more frequently recovered by sedimentation

QUANTITATIVE METHODS

In infections with hookworm as well as in infections with several other worms it is useful to know how many eggs are being passed per unit of stool or per unit of time These figures should be an indication of the number of worms present which has much to do with the severity of symptoms The methods which were used for this purpose were designed for survey work and they determine accurately the number of eggs being passed on the average by

CHAPTER LXV

TREATMENT OF INTESTINAL WORMS

J ALLEN SCOTT AND Z T BERCOVITZ

A RELATIVELY SMALL GROUP OF ANTHELMINTICS CONSTITUTE the drugs of choice for most physicians Only this group will be discussed here for it is only on rare occasions that one needs to consider the substitution of other drugs The appropriate drugs for use in infections located outside the intestinal tract have been considered under the discussion of each species of parasite A concise discussion of all the common anthelmintics now in use as well as those less frequently used in modern times together with a brief history of anthelmintic medication has been given by Faust (1939) Brown (1934) gives an excellent review of the practical methods of anthelmintic therapy for clinicians Chopra (1936) gives what is probably the best extensive discussion of this branch of therapeutics while the most recent developments especially from a chemical point of view are outlined by Wright and Harwood (1941)

GENERAL INSTRUCTIONS

(1) *Make a definite diagnosis* based on the demonstration of the typical ova larvae or segments of the parasite in question Do not institute treatment unless a definite diagnosis is made

(2) *Treat the patient* not the worm All drugs used in the treatment of worms are protoplasmic poisons Conditions of marked debilitation pregnancy lung liver kidney disease fevers including typhoid fever amebic or bacillary dysentery call for careful judgment to determine whether the parasitic infection is of more consequence than the underlying pathology All patients being treated with anthelmintics need careful supervision preferably in a hospital

(3) *Alcohol and fats* favor absorption of certain drugs especially carbon tetrachloride tetrachlorethylene chenopodium and consequently the danger of toxemia is increased

(4) *Purgatives* The use of a saline cathartic preparatory to treatment is favored by most authorities Magnesium sulphate is the drug of choice No purge should be given in the presence of a suspected appendicitis or of chronic

4 Allow to dry in air
5 Add equal parts of alcohol and ether for ten minutes
6 Allow to dry in air
7 Add Delafield s hematoxylin for seven to eight minutes
8 Wash in running water until blue color appears
9 Allow to dry in air Cover with balsam and coverslip

(NOTE O Connor s technique for counting microfilariae Take o mm of blood in a hemoglobin pipette and expel onto a glass slide Smear to 1 cm in diameter Allow to dry and stain as above Count microfilariae)

DIAGNOSIS OF PINWORM INFECTION

The most accurate means of diagnosing the presence of *Enterobius vermicularis* is the NIH swab This swab is made as follows a short glass rod with a rounded end is placed on a one inch square of cellophane and the latter is folded up around the rod and held in place with a small rubber band The rod is fastened in a cork so that it can be suspended in a test tube for purposes of transportation In use the folds of cellophane are scraped over the perianal rugae preferably before going to stool or washing in the morning The swab is then placed in the tube to prevent drying and sent to the laboratory There the cellophane is placed on a microscopic slide in a drop of liquid the rubber slid up and the cellophane allowed to flatten on the slide The preparation can be examined with or without a coverslip

Another swab introduced by Graham has not been given extensive testing but may be useful for certain types of office practice A strip of cellophane adhesive tape the ends of which are folded back is bent into a loop with the sticky side out and the folded ends held by forceps The perianal surface is then patted with the sticky material and the eggs adhering to it can be seen when the tape is placed on a microscopic slide and examined

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TABLE X

DRUGS USED IN TREATMENT OF INTESTINAL HELMINTHS

Drug	Maximum Adult Dose	Child Dose † per Year of Age	Used in Treatment of
Hexylresorcinol (Caprokol crystoids)	1 o gm	o 1 gm	Ascaris hookworm whipworm, pinworm Suggested also for tapeworm
Tetrachlorethylene	3 o cc	o 2 cc	Hookworm tapeworm
Oleoresin aspidium	6 o gm	o 4 gm (per 10 lbs body wt)	Tapeworm
Gentian violet (4½ hour enteric coating)	o 19 gm (3 grains daily)	o o1 gm (daily)	Pinworm Strongyloides *Clonorchis sinensis*
Oil of chenopodium	1 o cc	o 2 cc (from 4 yrs)	Ascaris hookworm whipworm pinworm
Carbon tetrachloride	3 o cc	o 2 cc	Hookworm tapeworm
Santonin Single dose Given as divided doses daily for 7 days	 o 2–o 3 gm o o6 gm	 o o1 gm (⅙ grain) o o25 gm	 Formerly used for all parasites Do not give on empty stomach — do not use oil cathartic [illegible]

Less toxic than carbon tetrachloride and equally eff[illegible]

† Total child dose should never exceed adult dose

against hookworm in fact for this purpose it is surpassed only by *tetrachlorethylene* Since the latter drug should not be given alone in the presence of *Ascaris* infections hexylresorcinol can be considered as good as any other safe treatment for hookworm when *Ascaris* is present Two doses of hexylresorcinol at an interval of two weeks will usually dispose of all the *Ascaris* and as many hookworms as a single dose of the much favored combination of tetrachlorethylene and chenopodium

Hexylresorcinol is the only drug which can be highly recommended for *Ascaris* or for hookworm in the presence of *Ascaris* It may also be frequently preferred to tetrachlorethylene for hookworm even when *Ascaris* is not present A second dose is given when the first is not entirely effective It has fair efficiency against tapeworms especially when given in repeated doses It has been successfully used against *Fasciolopsis buski* (McCoy and Chu 1937) and is as effective against whipworms as almost any drug on the market except *leche de higueron* which cannot be obtained everywhere The crystoids have been used successfully in combination with high enemas of the hexylresorcinol solution S T 37 for treatment of pinworm but for this purpose gentian violet is now considered equally effective and much more convenient to use

constipation In the case of the former condition anti parasitic treatment should be withheld until the diagnosis is definitely established In case of chronic constipation enemas must be given first to secure bowel movements in order to be sure that no obstruction exists Magnesium sulphate is usually given the evening before treatment and is repeated on the following morning in order to clear away the fecal matter so that the drug can act more directly on the parasite

A saline purge is usually given three or four hours after the administration of the last dose of the anthelmintic except in the case of hexylresorcinol when the salts are given twenty four hours later If vomiting occurs if the patient is toxic or other conditions indicate the purge may be given sooner Evacuation may be aided by the use of enemas especially if the patient shows signs of toxicity *No food should be given until the bowels have been evacuated* The exceptions to this rule are when hexylresorcinol is administered in which case food is withheld for four hours after the drug is given and when santonin is given in divided doses over a period of weeks In both of these exceptions the second saline purge is given twenty four hours following the administration of the last dose of the drug A further exception is gentian violet with which no purgative is needed

An acceptable routine which is of course subject to individual circumstances is to have the patient enter the hospital the evening before treatment and give him the benefit of careful physical and urine examinations Magnesium sulphate should be given at 9 P M At 6 or 7 o clock in the morning on an empty stomach the first dose of the drug is given and then subsequent doses are given each one half hour until the patient has taken the total amount The exception to this rule is in the case of hexylresorcinol in which the total amount is given at one time Three hours after the last dose a second saline purge is given unless the condition of the patient indicates earlier administration and evacuation of the bowels

The drug of choice is one which is effective in eradicating the parasites has a low degree of toxic effect on the host and will cause the least inconvenience to the patient Expense to the patient should also be taken into consideration

HEXYLRESORCINOL (CAPROKOL CRYSTOIDS)

Hexylresorcinol is the drug of choice for the treatment of infection with *Ascaris lumbricoides* and it is indicated especially in mixed infection with hookworm and *Ascaris* It may have some value in tapeworm and pinworm infections

Of all the drugs now in use hexylresorcinol comes nearest to fulfilling the requirements of a perfect anthelmintic for some worms No toxic symptoms have ever been reported following its use and there are no known contraindications It can be given without seriously interfering with the normal activity of the patient and repeated doses can be given when necessary without fear of cumulative toxicity It is as effective against *Ascaris* as any other drug including chenopodium and is also as effective as safe doses of the latter drug

The day following administration of the drug

Epsom salts in the same dosage as at first is optional

Diet is optional and as desired by the patient

Repeated Treatment for Tapeworms

The use of repeated doses has been of some success in the treatment of tape worms but not enough cases are on record to warrant a statement as to how effective it is The routine used is three full doses given as already indicated on alternate mornings with Epsom salts the night before Keep the diet light and give plenty of fruit juices and sugar

Treatment for Enterobius (Pinworms) with Hexylresorcinol

The pills are given according to the routine and after they are taken the bowel is cleaned out with a warm soapsuds enema A high enema of undiluted hexylresorcinol solution S T 37 is then introduced and retained for twenty minutes if possible Following its expulsion the anal region should be rinsed and dried to avoid irritation The treatment can be repeated in one or two weeks The whole family should be treated simultaneously in the case of pin worm infection

TETRACHLORETHYLENE (C_2Cl_4)

Tetrachlorethylene is the drug of choice for infections with hookworm that are uncomplicated with *Ascaris* The value of this drug for hookworm infec tions has been demonstrated by Hall and Schillinger (1925) and Lambert (1933) Its pharmacology and toxicity have been studied carefully by Lamson Robbins and Ward (19 9) The successful use of this drug in hookworm treat ment campaigns has been shown by Lambert (1933) who noted no toxic effects in 46 000 treatments in a single series In human beings it may be absorbed to a slight extent causing dizziness but this has been demonstrated to be due to its anesthetic properties and is not a symptom of intoxication (Lamson *et al* 1929) Sandground (1941) described two such cases and cited two others from the literature on the subject

Contraindications are the presence of roundworms *Ascaris lumbricoides* alcoholism concurrent treatment with arsenicals and gastro enteritis Chronic constipation should first be cleared up

Administration of Tetrachlorethylene

The most convenient form of administration for adults is in soft gelatin capsules each containing 0 5 cc (8 minims) For children the drug may be placed on a teaspoonful of sugar In mass treatment campaigns tetrachlor ethylene has usually been given in a saline purgative If so given it should be vigorously stirred until taken and any drops adhering to the glass should be washed down and taken with a little water

Method of Administration

The only caution to be observed is not to chew the pills which thus may cause mouth burns of an extremely irritating though not serious nature With care a physician can push the pills far enough back on the tongues of children who cannot otherwise swallow them so that they will be swallowed automatically Parents should not be entrusted with this responsibility because of the danger of pushing the pills into the trachea but most children can easily swallow them with water as they are not large in size

The effectiveness of hexylresorcinol will be greatly reduced unless the stomach is empty and unless food is withheld for about five hours after administration A saline purge the night before is essential to bring the worms into contact with the drug Purgation immediately after treatment is not necessary since this drug is not toxic To clear away any dead worms which are not passed spontaneously a saline purge may be given twenty four hours after treatment Re examination of the stool to determine the effectiveness of treatment should not be made for two weeks since worms have been passed as long as ten days after treatment After that time the same procedure may be repeated

Prescription and Method of Administration

As an anthelmintic hexylresorcinol should be prescribed only in the form of caprokol crystoids The caprokol solution and solution S T 37 do not have a high enough hexylresorcinol content to be of any value whatever when administered by mouth as a treatment for intestinal worms

The dosage is 0 1 gm per year of age up to ten years Each pill contains 0 20 gm Dosage should be regulated in accordance with the apparent age of children not their chronological age as follows

Under 3 years	1 pill (0 20 gm)
Ages 4 or 5 years	2 pills (0 40 gm)
Ages 6 or 7 years	3 pills (0 60 gm)
Ages 8 or 9 years	4 pills (0 80 gm)
Over 10 years and adults	5 pills (1 0 gm)

The *routine treatment* is as follows

The day before administration of the drug

1 00 P M give a purgative dosage of Epsom salts *Do not use castor oil*

Liquid diet and fluids for the afternoon and for supper

7 00 P M repeat the Epsom salts

The day of administration of the drug

No food or drink whatever

Give the total calculated dosage of hexylresorcinol at one time with a little water No cathartic drug is given on this day

No food or drink for five to six hours

Allow fruit juices with ample amounts of sugar after that time

Light diet for supper

the fetus to avoid the possibility of cysticercosis in the case of infections of *Taenia solium*)

Method of Administration

For two days before treatment fatty foods should be prohibited The day before treatment lunch is preferably omitted but sometimes a fat free liquid meal is allowed Black coffee and tea may be taken freely No supper is permitted and a purge of 15 to 30 gm of magnesium sulphate is given instead In the morning the drug is given according to one of two procedures either of which appears to be satisfactory but in any case the patient is kept in bed throughout the day Faust (1939 1941) recommends giving the oleoresin of aspidium on an empty stomach in the morning in three doses of 20 minims (1 3 cc.) each in capsules at half hour intervals for adults and three doses of 1 minim each per year of age for children Two hours later a saline purge is given and after one or two copious bowel movements food is permitted Magath and Brown (1927) recommend a second purge the first thing in the morning and when this has acted half of the following emulsion is given oleoresin of aspidium 6 cc powdered acacia 8 gm water to make 60 cc The second half is given one hour later For children the same emulsion is given in a total dose of 4 cc per 10 pounds of body weight Two hours after the second half is given 30 gm of magnesium sulphate are given in water Two hours later a large soapsuds enema is given to prevent the head of the worm from lodging in the colon If the patient vomits the drug immediately the same dosage is repeated by stomach tube Others (see Faust 1939) have given the drug by duodenal tube controlled by fluoroscopic examination using the same mixture given by Magath and Brown except that 30 cc of saturated solution of magnesium sulphate is substituted for an equal quantity of water and no post treatment purge is then necessary In any case an immediate check of the success of the treatment involves a search for the head in the material passed after the first purge as with tapeworms Some are of the opinion that the first movement should be passed with the buttocks immersed in a slop pail of warm water so that contact with a cold vessel will not cause the worm to contract and break giving the head a chance to attach again

GENTIAN VIOLET

Although the use of this drug as an anthelmintic cannot be said to be entirely out of the experimental stage successful treatment of several hundred cases has been reported and its general use under careful observation can be recommended It is much simpler to administer than hexylresorcinol enemas for pinworm and it is more effective for this purpose especially by reason of the greater likelihood of complete treatment being carried through (Wright and Brady 1940 D Antoni and Sawitz 1940 Faust 1941) It is the only known specific for *Strongyloides* infection (Faust 1938) and has been successfully used in the treatment of infection with the Chinese liver fluke *Clonorchis sinensis* (Faust and Yao 1926 Kawai 1937)

Dosage of Tetrachlorethylene

The children s dosage is 0 2 cc (3 minims) per year of age up to ten years The adult dosage is 3 0 cc Capsules may be given according to the following schedule

Under 4 years *apparent age*	0 5 cc (8 minims)
Ages 4 to 7 years	1.0 cc (2 capsules)
Ages 7 to 10 years	1 5 cc (3 capsules)
Ages 10 to 12 years	2 0 cc (4 capsules)
Ages 12 to 15 years	2 5 cc (5 capsules)
Over 15 and adults	3 0 cc (6 capsules)

Routine Treatment with Tetrachlorethylene

(1) The day before treatment the patient should not eat fat meat gravy oily dressings nuts butter cream or any other fatty foods

Do not allow any alcoholic beverages for twenty four hours before and after treatment

(2) The night before treatment allow only light or liquid diet without fatty substances

(3) 7 00 P M give saline purge *Do not use castor oil* Magnesium sulphate is the purge of choice but sodium sulphate or magnesium citrate may be used Give the saline purge in sufficient dosage to produce catharsis

(4) 7 00 A M on an empty stomach give the calculated dose of tetra chlorethylene with a little water

(5) One hour after the administration of the drug give a full cathartic dose of a saline purge

(6) The patient should lie down or at least remain quiet until the purgative has acted freely Then allow fruit juices with sugar and gradually give more food as desired but *fatty foods and alcoholic drinks must be avoided* for the next twenty four hours

OLEORESIN ASPIDIUM

Oleoresin aspidium has been used for many years for the removal of tape worms and can still be rated as the best available drug For dwarf tapeworm in children certainly the drug is too dangerous and hexylresorcinol is to be preferred Toxic symptoms include dizziness headache colored vision tempo rary blindness loss of reflexes while death has resulted from cardiac and respiratory paralysis Aspidium is irritating to the intestines and causes ab dominal distress nausea and vomiting and at times diarrhea while jaundice is common and may be accompanied by necrosis of the liver These manifesta tions are usually less severe if the patient is kept quiet throughout the treat ment and glucose is administered in adequate amounts Fatty foods of all kinds should be prohibited for forty eight hours before treatment and oil cathartics should be avoided because the drug is soluble in fats and may be absorbed Contraindications are gastro intestinal disease anemia and debility extreme old age infancy and pregnancy (although it may be necessary to risk sacrificing

TABLE XI

OUTLINE OF DOSAGES OF GENTIAN VIOLET FOR PINWORM TREATMENT

Apparent Age in Years	Tablets			Daily Dose		Number of Tablets in Entire Course
	Number	Size Gr.	To Be Taken Before	Gr.	Gm.	
1	1	3/20	Lunch	3/20	0.0	16
2	1	3/20	Lunch and supper	6/20	0.02	32
3 4 5		3/20	Each meal	9/20	0.03	50
6 7 8	2	3/20	Each meal	18/20	0.06	100
9 to 14	1	½	Each meal	1½	0.09	50
Over 15	2	½	Each meal	3	0.09	100

cially appropriate for bronchial and other extra enteric infections of *Strongyloides*. The drug is used in a 0.5 per cent solution made up in distilled water and filtered. Every third day 20 to 25 cc of this solution are administered, eight injections having been given without incident (Faust 1939). Temporary violet coloration of the skin and some fever may be expected. The patient must be hospitalized throughout the treatment; the injection must be made slowly in amounts and concentrations not to exceed those mentioned, and must not be repeated oftener than on alternate days.

CARBON TETRACHLORIDE (CCl_4)

At present there seems to be no good reason for using this toxic drug since the equally effective and non toxic tetrachlorethylene is available. The toxicity of carbon tetrachloride has been amply demonstrated by Lamson and Ward (1932), Lamson *et al.* (19 3), Minot (19 7 1931) and Minot and Cutler (1928 1930) and numerous other authors. Faust (1939) has reviewed the literature and gives the complete bibliography of this work.

OIL OF CHENOPODIUM

Oil of chenopodium is not recommended because of its toxic nature and because other safe drugs that are now available have proved equally effective. The drug has only two possible advantages over hexylresorcinol in the treatment of ascariasis. First, its lower cost, which is not sufficient to be of importance in private practice. Second, although tetrachlorethylene cannot be safely given for hookworm infection when *Ascaris* is also present, it has proved safe in combination with chenopodium. But the danger of chenopodium poisoning is still present and so hexylresorcinol is recommended for this purpose.

The dose of 1.5 cc is the maximum usually given for an adult. The doses for children are 0.3 cc for ages two to four years, 0.6 cc for ages five to nine and 0.9 cc for ages ten to fifteen years. It should not be overlooked, however, that doses of anthelmintics can be reduced to the point at which they will stimulate rather than kill such large worms as *Ascaris*, thereby causing penetra

Until recently the drug was given in enteric coated tablets but some persons passed them undissolved Now tablets with a coating which is timed to dissolve in four and one half hours are available and have proved more successful The drug is usually well tolerated although dizziness headache abdominal pain nausea and vomiting have occurred in a number of patients The effects have been transient and in most cases treatment has been resumed after an interval of a few days without further incident No serious reactions have been reported Contraindications are not definitely known but as a precaution the drug is usually not given to patients harboring *Ascaris* until that infection has been removed Nor is it used in cases which show evidence of cardiac hepatic renal or gastro intestinal disease Alcohol should not be taken during the treatment

Method of Administration

Tablets of gentian violet are prepared with enteric coatings which liberate the drug in about four and one half hours These are made by various manufacturers in the following doses for each tablet 0 0325 gm (½ grain) 0 016 gm (¼ grain) and 0 0097 gm (3/20 grains)

For pinworm in children weighing less than 100 pounds the dosage is 0 03 5 gm (½ grain) three times daily about one hour before meals for fourteen days The treatment is discontinued for seven days and the above routine is repeated For those weighing more than 100 pounds the procedure is 0 06 gm (1 grain) one hour before meals for seven days no therapy for seven days and then repeat In a carefully controlled study by D Antoni and Sawitz (1940) approximately 90 per cent cures of pinworm infection were obtained by this method of treatment This routine has been used by Bercovitz for the past two years in private practice and with a large number of clinic patients with pinworm infections with results approximating those reported by D Antoni and Sawitz

Another method of administration is as follows The total daily dosage for an adult is 0 10 gm (3 grains) For children the total daily dosage is calculated on the basis of 0 0097 to 0 01 gm (3– 0 grains) per year of apparent age The medicine is given in divided doses about one hour before meals according to Table XI For *Strongyloides* the entire course is taken consecutively For pinworm the treatment is taken for 8 days it is then discontinued for 7 days after which it is continued until the quantity indicated has been taken

For the treatment of *Clonorchis* Chinese liver fluke the same dosage is prescribed as for *Strongyloides* and the same instructions are given but if the drug is well tolerated the treatment is continued twice as long

For refractory cases of *Strongyloides* which are not cured by this treatment Faust (1941) now recommends repeating the same course and dosage but using tablets with a one and one half hour coating Formerly (1939) he used 25 cc of a 1 per cent aqueous solution of gentian violet administered very slowly through a duodenal tube placed in position under a fluoroscope and left in position for an hour after treatment Faust (1939) reported on the use of intravenous injections of gentian violet for refractory cases This is espe

(3) At bedtime the patient should take the calculated dosage

(4) In the morning the cathartic should be taken at least one half hour before eating breakfast

Divided Dose Method Dosage 0 01 gm (1/6 grain) each of santonin and calomel for each three years of age up to an adult dose of 0 065 gm (1 grain) Dosage to be taken several hours after breakfast on five successive days with dietary restrictions as outlined but no catharsis in addition to the calomel if the case reacts normally Treatment should be stopped if toxic symptoms appear

LECHE DE HIGUERON

Leche de higueron is the crude sap of a bastard fig tree which has been used as an anthelmintic in Central and South America for many years No satisfactory means of preservation has yet been devised and the use of the drug is confined to regions where it can be obtained fresh or transported under refrigeration A test by Caldwell and Caldwell (1929) showed it to be an efficient drug for the treatment of trichuriasis for which there is no other satisfactory treatment Faust (1939) has reported several hundred cases treated with this drug without ill effects He recommends a saline purge the night before treatment then in the morning on an empty stomach 2 ounces (60 cc) of the drug followed by a half glass of water Two hours later another saline purge is given and food allowed after this has acted He tested a preserved product sold under the name of *Higueronia* and found it to be about 75 per cent as efficient as the refrigerated sap

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tion of the intestinal wall migration into the stomach and in some case subsequent blocking of the larynx or nares

OIL OF CHENOPODIUM WITH TETRACHLORETHYLENE

Since it may be dangerous to give tetrachlorethylene to patients with *Ascaris*, it has been customary to give such cases a combination of these two drugs Since the dosage of chenopodium is thereby reduced the danger of toxic effects is lessened but if it is true that many of the fatalities from chenopodium poisoning have been due to idiosyncrasies this danger is still present The use of hexylresorcinol crystoids is recommended for such cases

The usual dosage in the combined treatment is 0 05 to 1 0 cc. of chenopodium and 2 cc of tetrachlorethylene Treatment should be given on an empty stomach it should be followed by a strong saline purge and no food should be allowed until the bowels have moved freely Alcohol should be prohibited during the treatment period Contraindications are alcoholism cardiac or renal diseases gastro-enteritis The treatment should not be administered during pregnancy or to very young children In constipated cases attention should be given to clearing up the stasis before treatment In any case a free bowel movement should be produced within three hours after treatment

SANTONIN

Santonin is a time honored anthelmintic which has undoubtedly been successful in the removal of *Ascaris* from many children Under modern testing methods however it has been rated as a rather inefficient drug for this purpose since in most cases it removes only a small proportion of the worms present Moreover recent work has shown that it has definite toxic properties which cause colored vision nausea abdominal distress vomiting diarrhea hematuria convulsions and rarely even coma and death There are no essential contraindications but alcohol and fats are usually prohibited Purgation is usually accomplished by giving an equal amount of calomel with each dose but a saline purge may be given a few hours later if necessary Some think that saline purgation is to be preferred and that divided doses are more effective

Method of Administration

Single Dose Method Dosage 0 01 gm (1/6 grain) each of santonin and calomel for each year of age up to an adult dose of 0 2 gm (3 grains) The saline cathartic is optional

Routine of treatment

(1) Do not allow the patient to take alcoholic beverages during the day of treatment or the day after

(2) Do not allow the patient to eat fat meat gravy fried foods nuts butter cream or other fatty foods during the day The meal should be planned so that a light supper will be eaten about five hours before retiring and nothing should be eaten afterward

SECTION TEN

TROPICAL SNAKES AND POISONOUS INSECTS

CHAPTER LXVI

SNAKES AND SNAKE POISONING

JAMES A. OLIVER

INTRODUCTION

THE IMPORTANCE OF SNAKE BITES AS A SERIOUS MEDICAL problem has been greatly exaggerated not only among laymen but also among doctors who have had little experience with such cases. This statement is by no means intended to imply that snake bites are of no importance or that they do not involve serious consequences. The bite of a venomous snake is indeed a serious medical problem which calls for prompt, vigorous, and *accurate* treatment. But the incidence of snake bite cases in most regions, including the tropics, is far lower than commonly thought. It is the responsibility of the competent medical man to familiarize himself with the poisonous snakes of the regions in which he is stationed, to know adequate preventive measures and proper treatment, especially in the tropical regions where the more dangerous species are found. It is far beyond the scope of this brief account to detail the various ramifications of the snake poison problems or to make provision for the identification of all species of poisonous snakes. However, it is hoped that the major points are covered sufficiently to give the experienced doctor an intelligent background for handling snake bite cases.

Data on the incidence of and mortality from snake poisoning are difficult to obtain, and no accurate figures are available to give the true picture. Many reports and estimates have been given for various regions of the world, but few of these are considered to be accurate. The estimate of 0,000 deaths a year from snake poisoning in India alone is probably exaggerated on the basis of comparison with comparable adjacent areas. The Antivenin Institute of America attempted to gather information of this sort for the United States. The recorded number of bites was between five and six hundred a year in 19 8 and 19 9. These figures have been estimated to represent about one third of the total number of bites actually occurring in the United States, giving an estimated total number of bites between 1,500 and 1,800. The mortality rate in these bites runs slightly above 5 per cent, indicating an annual death rate of about one hundred persons in the United States. Hutchison (1930) gives the actual number of cases reported to the Antivenin Institute in 19 9 as 482, of

many of the larger more active forms include some of the world s most dangerous snakes This family has its greatest development in Australia but several well known forms occur in the East Indies Asia and Africa Only the coral snakes are representative of this group in the Americas

Family HYDROPHIIDAE

The members of this family are the sea snakes They are very similar to the forms of the preceding family and for a long time were considered as properly belonging to that family They differ from the ELAPIDAE in possessing certain modifications which have accompanied their adaptation to a marine life chiefly the flattening of the tail from side to side to assist in swimming and the loss of broad abdominal scales The sea snakes possess the same type of relatively short erect immovable front fangs Although the venom of some species is among the most toxic known natives in areas where the sea snakes occur do not fear them Because of their aquatic habits they are seldom encountered and when they are they are slow to bite Sea snakes occur most abundantly in the seas of northern Australia and southern Asia One wide ranging form has reached the east coast of Africa and the west coast of America They frequent the inshore or estuary waters rather than the open ocean One species is found in an inland lake on the Philippines Bites from sea snakes are relatively rare

Family VIPERIDAE

The members of this family are known as the true vipers to distinguish them from the CROTALIDAE All possess long curved movable front fangs which can be erected when the snake strikes They lack the sensory pit between the eye and nostril which characterizes the pit vipers of the next family The VIPERIDAE thrive best in Africa and a large number of species flourish in Europe None is found in the Americas or in Australia

Family CROTALIDAE

The pit vipers have the same type of efficient poison injecting apparatus as that possessed by the true vipers but they are easily distinguished by the presence of the sensory pit situated between the eye and nostril (Fig 108) The members of this family are most abundant in the Americas southeastern Asia and the East Indies but they are unknown in Australia in Africa and in Europe except for the extreme eastern portion

A key for the identification of these families utilizes the following characters

A Short erect *immovable* front fangs	
a Tail round not flattened or rudder shaped	ELAPIDAE
aa Tail flattened from side to side rudder shaped	HYDROPHIIDAE
AA Long *movable* front fangs	
a No facial pit between eye and nostril	VIPERIDAE
aa A facial pit between eye and nostril	CROTALIDAE

which 28 were fatal Clark (1942) in discussing the snake bite situation in Central American states In all the wide spread banana plantations of the United Fruit Company in Central America their medical records show 23 snake bite accidents per 100 000 population per annum Though admittedly incomplete these figures suggest the relative infrequency of snake bite cases in two sections of the Americas

The highest mortality rate occurs in the tropical and subtropical regions where the Indo Oriental area has probably the highest percentage of fatal bites as well as the highest incidence of snake bite The higher mortality rate in tropical regions is not necessarily due to a greater population density in the venomous snakes but to the presence of more dangerous snakes the lack of preventive measures on the part of natives and the lack of medical treatment in many cases of snake bite

With the increase in knowledge of serum therapy and the increased efficiency in mechanical snake bite treatment the mortality rate has been lowered considerably in the last decade

CLASSIFICATION AND IDENTIFICATION OF POISONOUS SNAKES

It is the responsibility of the doctor to know what poisonous snakes occur in his vicinity because this knowledge is essential to proper treatment In order to know which snakes are poisonous the doctor does not need to become a trained herpetologist as there are usually only a few different kinds of venomous snakes in any one area

The important venomous snakes of the world belong to four families all the members of which possess enlarged hypodermic like *front* fangs by which the venom is injected The four families are conveniently arranged in two groups the PROTEROGLYPHA (including the ELAPIDAE the cobras and allies and the HYDROPHIIDAE the sea snakes) and the SOLENOGLYPHA (including the CROTALIDAE the pit vipers and VIPERIDAE the true vipers)

In the PROTEROGLYPHA the fangs are relatively short and are rigidly fixed in an erect position to the anterior part of the upper jaw The SOLENOGLYPHA on the other hand are equipped with long curved fangs which are set in movable bones and which can be folded back against the roof of the mouth when at rest or can be raised in an erect position when the snake strikes

Family ELAPIDAE

This is the largest family of poisonous snakes with representatives on all continents except Europe and Antarctica The ELAPIDAE include approximately half of all the known species of front fanged snakes The members of this family show much variation in form and habits although in external characters they often closely resemble common harmless species These snakes can readily be recognized by the relatively short erect immovable front fangs In size the various species range from little more than a foot in length to the giant among the poisonous snakes the king cobra which attains a length of 18 feet The smaller often secretive species are of no medical importance but



Fig 109 Skull showing the teeth of the *Solenoglypha* Note enlarged front fangs



Fig 110 Skull showing the teeth of the *Proteroglypha* Note enlarged front fangs (Courtesy of American Museum of Natural History)



Fig 111 Skull of a harmless form (*Aglypha*) Compare with Figures 109 and 110 noting the lack of enlarged front fangs as in the poisonous form.

The members of these four families of poisonous snakes are characterized by the possession of elongate hollow teeth for the injection of venom These elongate teeth are the fangs the possession of which readily distinguishes these

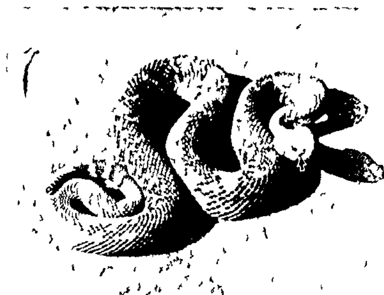


FIG 108 Rattlesnake showing sensory pit of CROTALIDAE Note its position between and slightly below the eye and nostril (Courtesy of C M Bogert)

venomous snakes from their harmless relatives The characteristic arrangement of teeth in the skulls of the PROTEROGLYPHA and the SOLENOGLYPHA as compared with that of a harmless species (*Aglypha*) is shown in Figures 109 to 111

The venomous snakes possess one or two functional fangs on each side of the mouth These are shed more or less periodically but the snake is normally never without fangs As the old tooth is about to be shed the new one takes its place alongside and for a brief period two functional fangs are present on that side A few harmless species mostly aboreal forms that feed on birds have anterior teeth which are markedly elongate but these forms should not be confused with the poisonous species as they possess more than one or two elongate solid teeth on each side of the mouth The elongate teeth grade in an even series from the front to the back of the mouth and the teeth of the lower jaw are approximately as long as those of the upper jaw

A doctor stationed in any area can readily learn to recognize the poisonous species in his vicinity through the collection and examination of the heads of the various local forms A precautionary remark should be added to the effect that the heads should not be examined immediately after the snake is killed unless extreme care is taken Snakes are capable of marked reflex action for a prolonged period after death and a number of bites have occurred during the examination or handling of supposedly dead specimens



FIG. 109. Skull showing the teeth of the *Solenoglypha*. Note enlarged front fangs.



FIG. 110. Skull showing the teeth of the *Proteroglypha*. Note enlarged front fangs. (Courtesy of American Museum of Natural History.)



FIG. 111. Skull of a harmless form (*Aglypha*). Compare with Figures 109 and 110, noting the lack of enlarged front fangs as in the poisonous form.

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In looking at the natural heads to determine which are poisonous and which are not we notice that the tooth structure does not appear as clearly as that shown in the skull figures The fangs in the natural condition are surrounded



FIG 113 *Proteroglypha* (poisonous) showing natural appearance of the mouth Note relatively short exposed fang

by a fleshy sheath the *vagina dentis* By dissecting away the protective sheath we can expose the fang and can note its character After brief experience in the examination of heads the doctor can recognize poisonous species without dissection of the fang sheath by merely noting the characteristic fleshy knob or ridge at the fang site However positive identification can be made only by observing the hollow fang preferably under magnification The con



FIG 112 *Solenoglypha* Natural appearance of mouth (poisonous) showing the fang sheath on one side of the mouth and the exposed long curved fang on the other

dition of the natural heads is shown in Figures 112 to 114 These photographs show the lower aspect of the upper jaw in the two types of front fanged snakes and in a harmless species The fleshy sheath is dissected away on one side of the jaw in each of the poisonous forms to expose the fangs

Throughout this account the discussion of poisonous snakes is confined to four families of front fanged snakes The important venomous snakes from the standpoint of human snake bite cases belong to these families There are however other poisonous snakes In the case of a number of species one or more of the teeth in the back of the upper jaw have become elongate and grooved for the injection of venom These snakes are referred to as the rear fanged snakes or OPISTHOGLYPHA Their poison injecting apparatus is not as efficient as that of the front fanged snakes and often necessitates chewing to insure penetration of the rear fangs The snakes of this group do not present a serious snake bite problem for human beings with the possible exception of the African boomslang (*Dispholidus typus*) Most of the rear fanged snakes are either too small or else their venom is too mild to have a lethal effect on men

GEOGRAPHICAL DISTRIBUTION OF IMPORTANT POISONOUS SNAKES

It has already been emphasized that it is important for the physician to be familiar with the types of poisonous snakes commonly found in the area in which he is working Only through a knowledge of these can he intelligently handle the snake bite problem With such information at his dispatch he knows which snakes in his region are responsible for the greatest number of bites and which produce the highest mortality rate he knows the general effects which are produced by the different venoms and he knows what specific or polyvalent serums are of value in a particular case

From this standpoint it is worth while to discuss briefly the geographical distribution of the more important species and to mention certain areas notable for their lack of poisonous species Snakes like all animals and plants show interesting peculiarities in their distribution for each species has a circumscribed geographical range Each continent and island has characteristic fauna and flora reflecting its geographical position and geological history Islands remotely removed and well isolated from adjacent continents tend to have smaller floras and faunas than those islands which are closely connected to the adjacent continent Therefore a number of islands large and small completely lack terrestrial poisonous snakes With the exception of Martinique St Lucia and Trinidad the West Indies have no dangerously poisonous snakes and there are none on the islands of Ireland Madagascar New Zealand or Hawaii With the exception of the Bismarck Archipelago the Solomon Islands and the Fiji Islands the oceanic islands of the Pacific Ocean *east* of the Philippines and New Guinea are free of terrestrial venomous snakes While these islands are free of terrestrial poisonous snakes venomous sea snakes may be found on their shores



Fig 114 *Aglypha* (harmless) Note rows of teeth and absence of fangs or fang sheath Compare with Figures 112 and 113

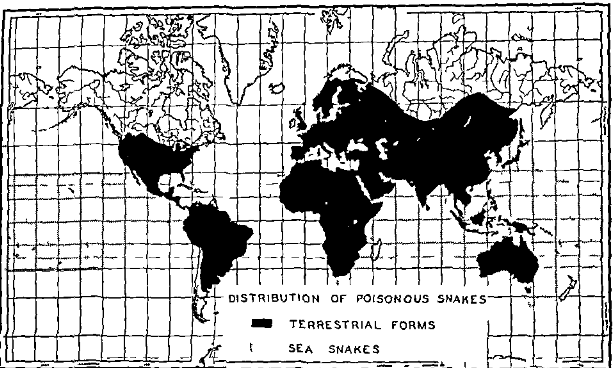


Fig 11, D stribut on of po sonous snakes throughout the v orld

North America

The CROTALIDAE which are the predominant poisonous snakes are represented by numerous species of rattlesnakes (*Crotalus* and *Sistrurus*) the copperhead (*Agkistrodon mokasen*) and the water moccasin or cotton mouth (*Agkistrodon piscivorus*) The ELAPIDAE are represented by two species of coral snakes (*Micrurus* and *Micruroides*) in the southern United States with additional species in Central and South America

Some of the thirteen species of rattlesnakes inhabiting the United States are found in practically every part of this country though in recent years they have been exterminated locally through man s activities They range in size from the two foot pygmy rattler to the large Florida diamond back and the western diamond back which attain a length of slightly more than 7 feet The copperhead with an average length of about 3 feet ranges over the eastern half of the United States and as far west as southern Texas The water moccasin lives in the swampy regions of the Southeast the Mississippi Valley and west into central Texas The rattlers copperheads and the water moccasin have a predominantly hematoxic venom The copperhead is responsible for more snake bite cases in the United States than any other species though the bite is rarely fatal except in children The western diamond back rattler (*Crotalus atrox*) ranks first among the United States species in causing the greatest number of fatal bites

The coral snakes found in the southern part of the United States and Mexico are relatively small and slender with bright coloration in the form of red yellow and black rings They secrete a predominantly neurotoxic venom but because of their small size and secretive habits few cases of coral snake bites are reported

Central America

Both the CROTALIDAE and ELAPIDAE are well represented by a number of species Several species of rattlesnakes inhabit Mexico some representatives of this group occur in nearly every part of the country In southern Mexico one race of the tropical rattlesnake the Central American rattlesnake (*Crotalus d durissus*) occurs This form ranges south to Panama and belongs to one of three species of rattlesnake inhabiting Central and South America It attains a large size and has a powerful neurotoxic element in its venom Other members of the family CROTALIDAE occurring in Central America are the Mexican or tropical moccasin (*Agkistrodon bilineatus*) which ranges from northern Mexico to Honduras and various species of the genus *Bothrops* (=*Trimeresurus of some* authors) which has representatives throughout Central and most of South America The best known member of this latter genus is the dreaded fer de lance or Barba ammarilla (*Bothrops atrox*) which may reach a length of 8 feet and which possesses a powerful hematoxic venom Other members of this genus include several forms of the hog nosed pit vipers and the mano de Piedra or jumping pit viper (*Bothrops nummifer*) Clark (1942) in discussing the snake bite problem in Central America states that the fer de lance is

the species except one belong to the genus *Vipera* of the family VIPERIDAE The single exception is a species of pit viper *Agkistrodon halys* which barely reaches extreme eastern Europe near the Caspian Sea between the Volga and Ural Rivers The species of *Vipera* are for the most part small in size rarely exceeding [illegible] feet in length and the effect of their predominantly hematoxic venom is seldom fatal in man The genus ranges as far north as northern Scot land in the British Isles and beyond the sixty seventh degree north latitude in Scandinavia In general the larger more dangerous forms occur in southern Europe in the countries bordering the Mediterranean and it is here that most of the fatalities are recorded

Africa

On this continent is found the best development of the VIPERIDAE as well as a number of highly dangerous representatives of the ELAPIDAE The former are represented by the well known heavy bodied and large headed puff adder (*Bitis lachesis* [= *B arietans* of authors]) the Gaboon viper (*Bitis gabonica*) and the rhinoceros viper (*Bitis nasicornis*) The first of these is widely dis tributed from South Africa to southern Arabia while the two latter species occur in equatorial Africa Other African VIPERIDAE include the saw scaled viper (*Echis carinatus*) which inhabits a wide range of territory over North Africa Arabia and eastward into India the night adders of the genus *Causus* occurring over most of Africa south of the Sahara and the horned viper (*Aspis* [= *Cerastes* of authors] *cornutus*) of the deserts of North Africa There are additional species of VIPERIDAE which occur in Africa but the forms men tioned above are the ones of major importance The venom of the VIPERIDAE is predominantly hematoxic except for the Gaboon viper which has a power ful neurotoxic element

The representatives of the ELAPIDAE include several species of cobras of the genus *Naja* the mambas of the genus *Dendroaspis* (= *Dendraspis* of au thors) and the South African ringhals (*Hemachatus* [= *Sepedon* of authors] *haemachatus*) The cobras which are found throughout the greater part of Africa rarely attain a length of more than 6 feet They include forms which have the ability to eject or spit their venom at their enemies directing it toward the eyes where it causes intense pain and temporary blindness The ringhal of South Africa can also eject its venom in the same manner as the spitting cobras The mambas three species occur throughout most of Africa south of the Sahara These are long slender snakes attaining a length over 7 feet They are extremely quick in their movements possess exceptionally long fangs for members of the ELAPIDAE and carry a powerful and predomi nantly neurotoxic venom A number of less important species of ELAPIDAE also occur in Africa Two of these are worthy of mention because of their habits the arboreal cobras of the genus *Pseudohaje* inhabiting the forests of central and west Africa and the aquatic cobras of the genus *Boulengerina* inhabiting the rain forests of equatorial Africa from the Cameroons to Lake Tanganyika These ELAPIDAE all possess a predominantly neurotoxic venom

the cause of nearly all our serious snake-bite cases and that about 80 to 85 per cent of poisonous snake-bite cases are bound to be the result of some species of *Bothrops*

The renowned bushmaster (*Lachesis muta*) one of the largest of the pit vipers occurs only in the extreme lower part of Central America and will therefore be mentioned further under South America

The ELAPIDAE are again represented by the coral snakes which are generally similar to those in the United States though some species attain a much larger size and consequently are more dangerous through their ability to inject a larger quantity of venom It should be noted that the color characters so frequently described in popular books to distinguish the coral snakes of the United States from similarly colored harmless species *are not* applicable to all Central and South American coral snakes For example one species of South American coral snake is nearly uniform black and is without bands

South America

The major poisonous snakes of South America are generically the same as those of Central America with different species or races representing these genera *except that no member of the genus Agkistrodon occurs in South America* The South American rattlesnake (*Crotalus durissus terrificus*) is a wide-ranging race closely allied to the Central American form This species attaining a length of 5 or 6 feet is capable of inflicting a very serious bite because of its predominantly neurotoxic venom a character unusual among the rattlers

Tall tales of the tropics have raised the bushmaster to the questionable position of Lord High Executioner among the snakes of our American tropics. There is no question that this pit viper reputedly reaching a length of 11 or 12 feet is capable of inflicting a highly dangerous bite with its predominantly hematoxic venom However from all available information it is infrequently encountered and therefore not a common contributor to the snake bite problem although it is by no means a species to be ignored

The genus *Bothrops* is represented by numerous species including several hog nosed pit vipers several arboreal or tree pit vipers the fer-de-lance (*Bothrops atrox*) the vibora de la cruz (*Bothrops alternata*) the jararaca (*Bothrops jararaca*) and the white-tail jararaca (*Bothrops neuwiedii*)

The coral snakes of the genera *Micrurus* and *Leptomicrurus* are represented by a number of species some of which attain a much larger size than their relatives in North America While the North American coral snakes do not present a serious snake-bite problem some of the South American species are of sufficient importance that a special serum has been prepared to combat their venom

Europe

Although poisonous snakes occur throughout most of Europe, with the notable exception of Ireland the poisonous snake problem is not serious All

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Africa

On this continent is found the best development of the VIPERIDAE as well as a number of highly dangerous representatives of the ELAPIDAE The former are represented by the well known heavy bodied and large headed puff adder (*Bitis lachesis* [= *B arietans* of authors]) the Gaboon viper (*Bitis gabonica*) and the rhinoceros viper (*Bitis nasicornis*) The first of these is widely dis tributed from South Africa to southern Arabia while the two latter species occur in equatorial Africa Other African VIPERIDAE include the saw scaled viper (*Echis carinatus*) which inhabits a wide range of territory over North Africa Arabia and eastward into India the night adders of the genus *Causus* occurring over most of Africa south of the Sahara and the horned viper (*Aspis* [= *Cerastes* of authors] *cornutus*) of the deserts of North Africa There are additional species of VIPERIDAE which occur in Africa but the forms men tioned above are the ones of major importance The venom of the VIPERIDAE is predominantly hematoxic except for the Gaboon viper which has a power ful neurotoxic element

The representatives of the ELAPIDAE include several species of cobras of the genus *Naja* the mambas of the genus *Dendroaspis* (= *Dendraspis* of au thors) and the South African ringhals (*Hemachatus* [= *Sepedon* of authors] *haemachatus*) The cobras which are found throughout the greater part of Africa rarely attain a length of more than 6 feet They include forms which have the ability to eject or spit their venom at their enemies directing it toward the eyes where it causes intense pain and temporary blindness The ringhal of South Africa can also eject its venom in the same manner as the spitting cobras The mambas three species occur throughout most of Africa south of the Sahara These are long slender snakes attaining a length over 7 feet They are extremely quick in their movements possess exceptionally long fangs for members of the ELAPIDAE and carry a powerful and predomi nantly neurotoxic venom A number of less important species of ELAPIDAE also occur in Africa Two of these are worthy of mention because of their habits the arboreal cobras of the genus *Pseudohaje* inhabiting the forests of central and west Africa and the aquatic cobras of the genus *Boulengerina* inhabiting the rain forests of equatorial Africa from the Cameroons to Lake Tanganyika These ELAPIDAE all possess a predominantly neurotoxic venom

the cause of nearly all our serious snake bite cases and that about 80 to 85 per cent of poisonous snake bite cases are bound to be the result of some species of *Bothrops*'

The renowned bushmaster (*Lachesis muta*) one of the largest of the pit vipers occurs only in the extreme lower part of Central America and will therefore be mentioned further under South America

The ELAPIDAE are again represented by the coral snakes which are generally similar to those in the United States though some species attain a much larger size and consequently are more dangerous through their ability to inject a larger quantity of venom It should be noted that the color characters so frequently described in popular books to distinguish the coral snakes of the United States from similarly colored harmless species *are not* applicable to all Central and South American coral snakes For example one species of South American coral snake is nearly uniform black and is without bands

South America

The major poisonous snakes of South America are generically the same as those of Central America with different species or races representing these genera except that no member of the genus *Agkistrodon* occurs in South America The South American rattlesnake (*Crotalus durissus terrificus*) is a wide ranging race closely allied to the Central American form This species attaining a length of 5 or 6 feet is capable of inflicting a very serious bite because of its predominantly neurotoxic venom a character unusual among the rattlers

Tall tales of the tropics have raised the bushmaster to the questionable position of Lord High Executioner among the snakes of our American tropics There is no question that this pit viper reputedly reaching a length of 11 or 12 feet is capable of inflicting a highly dangerous bite with its predominantly hematoxic venom However from all available information it is infrequently encountered and therefore not a common contributor to the snake bite problem although it is by no means a species to be ignored

The genus *Bothrops* is represented by numerous species including several hog nosed pit vipers several arboreal or tree pit vipers the fer-de lance (*Bothrops atrox*) the vibora de la cruz (*Bothrops alternata*) the jararaca (*Bothrops jararaca*) and the white tail jararaca (*Bothrops neuwiedii*)

The coral snakes of the genera *Micrurus* and *Leptomicrurus* are represented by a number of species some of which attain a much larger size than their relatives in North America While the North American coral snakes do not present a serious snake bite problem some of the South American species are of sufficient importance that a special serum has been prepared to combat their venom

Europe

Although poisonous snakes occur throughout most of Europe with the notable exception of Ireland the poisonous snake problem is not serious All

Borneo Sumatra Java Lombok Flores and Ombaai Some of the Asiatic cobras have like the African spitting cobra acquired the ability to eject the venom for a distance of several feet aiming at the eyes Such spitters occur in Ceylon Burma the Malay Peninsula Indo China Sumatra and Java This venom in the eyes produces a marked burning sensation and may result in blindness The cobras are usually readily identified by their habit of raising the anterior portion of the body into a nearly vertical position and spreading the neck to form the hood However some cobras do not spread the hood before striking

In addition to the cobras the ELAPIDAE are represented by several species of kraits of the genus *Bungarus* Kraits occur in India Ceylon Burma China Indo-China Siam the Malay Peninsula the Philippines Borneo Sumatra Nias Java and Celebes Though some species are slow to bite and appear quite tame some kraits are of importance in the snake bite problem of southern Asia Shaw Shebbeare and Barber (191) say that the common krait is not aggressive but probably responsible for more deaths than any other snake in India The reason for this is partly its habit of frequenting houses in search of frogs and mice and partly the extreme virulence of its venom four times that of the cobra

Some of the forms of the important venomous species of Asia it will be noted are present in some of the East Indies islands Because of their position these islands form a pathway between Asia and Australia on which we find elements of both faunas The islands adjacent to Asia have Asiatic species while those closest to Australia have species derived from that continent For this reason it has been considered best to discuss the two entities under the continents with which they have their affinities In general those islands west of 127 degrees east longitude have poisonous species similar to or in common with those of the Asiatic mainland while those east of this line are Australian in nature and include only members of the ELAPIDAE

Australia

The poisonous terrestrial snakes of this continent are all members of the family ELAPIDAE It is here that we find the greatest development of this family with more than sixty forms However many of these are so small so rare or have such highly secretive habits that they are of no concern to human beings The important poisonous snakes of Australia are the death adder (*Acanthophis antarcticus*) which also occurs on the islands of Jobi New Guinea Ceram Ke and Aru the tiger snake (*Notechis scutatus*) only in Australia several species of *Denisonia* in Australia Tasmania and the Solomon Islands the brown snake (*Demansia textilis*) and other species of the same genus occurring throughout Australia and the snakes of the genus *Pseudechis* including the black snake (*Pseudechis porphyriacus*) in Australia and the giant brown snake or taipan (*Pseudechis scutellatus*) of Australia and New Guinea This last form which attains a length of 9 feet is the largest poisonous snake of Australia and New Guinea Other ELAPIDAE which are of interest

Asia

The important snakes of this continent are those occurring in the tropical and subtropical areas Two of the VIPERIDAE mentioned under Africa extend their range into Asia the puff adder which occurs in southern Arabia and the saw scaled viper which occurs in Arabia and India The outstanding representative of the VIPERIDAE in southern Asia is the daboia ticpolonga or Russell s viper (*Vipera russellii*) which may attain a length of 5 feet This snake is frequently listed as one of the most important contributors to snake bite fatalities in India Ceylon Burma Siam southern China Formosa Sumatra and Java The venom of this species is highly hematoxic with powerful cytolytic properties

The CROTALIDAE have a number of species in southeastern and eastern Asia and on the adjacent East Indies From the standpoint of the snake bite problem few of the CROTALIDAE attain the prominence of Russell s viper or the important ELAPIDAE of the continent The species of pit vipers from this area belong to two genera *Agkistrodon* and *Trimeresurus* and include tree living forms with prehensile tails Representatives of these genera occur throughout southern Asia from the Caspian Sea eastward to Japan south in India Ceylon Burma Siam Indo China Malaya the adjacent East Indies Formosa the Philippines and the Riu Kiu (Liu Chiu) Islands Because of their small size their disinclination to bite or the comparatively low toxicity of their predominantly hematoxic venom most of these species are seldom responsible for snake bite fatalities However the figures quoted by Maass (1934) for Formosa *indicate that two species of pit vipers Trimeresurus gramineus* and *Trimeresurus mucrosquamatus* are responsible for the greatest number of snake bite cases and for a large number of fatalities on that island The former species is responsible for the highest incidence of bites but has a mortality percentage of only 1 27 per cent the latter has a somewhat lower incidence of bites but a mortality percentage of *9 14*

Other pit vipers worthy of consideration are the habu (*Trimeresurus flavoviridus*) of the Riu Kiu Islands *Agkistrodon rhodostoma* of Siam the Malay Peninsula Sumatra and Java *Agkistrodon acutus* of China and Formosa and the widespread *Agkistrodon halys* occurring from eastern Europe in the vicinity of the Caspian Sea across Asia to Japan thence south to the Pescadores Islands and the Yangtze Valley

The representatives of the ELAPIDAE include the king cobra (*Hamadryas hannah*) of Burma southern China the Malay Peninsula Indo China Sumatra Borneo Java Celebes and the Philippine Islands This snake is well known not only because of its large size but also because of its aggressive nature and powerful neurotoxic venom The smaller but equally *well known* Indian or Asiatic cobra (*Naja naja*) is far more common than its larger relative The Asiatic cobra has several pattern varieties and color phases which are to be found in its wide range in India Ceylon Burma southern China Formosa Indo China Siam the Malay Peninsula the Philippine Islands

muscles The muscle fibers are arranged so that the contraction of the temporal muscles in the act of biting expels the poison from the gland An excretory canal emerges from the anterior portion of the gland and conducts the venom forward into the base of the fang The fangs are borne by the maxillary bone and they may be movable as in the SOLENOGLYPHA or relatively stationary as in the PROTEROGLYPHA Through the fangs the venom is introduced subcutaneously intramuscularly or very rarely directly into a vein Venom may be absorbed through the conjunctiva and through breaks in the skin or mucous membranes though it is rarely absorbed in lethal quantities through these paths

Quantity

The quantity of venom secreted in the act of biting varies according to the species the size age and the condition of the snake at the time of the bite In general the larger the snake the greater the quantity of venom injected though there are numerous exceptions to this generality The amount of venom injected depends on the time interval since the last bite the venom glands usually requiring approximately two weeks to regain maximum capacity of venom In a normal bite a snake does not expel its full quantity of venom but only a small portion and is still capable of inflicting a fatal bite Evidence indicates that an enraged snake injects a greater quantity of venom than one which has not been angered prior to biting The amount of venom released during a spontaneous bite is greater than that obtained by investigators through milking or forced expulsion of the venom The following figures give some indication of the approximate quantity of dry venom obtained at a single extraction from a number of common poisonous snakes

	Mg
A *North American Species*	
Copperhead	45–65
Water moccasin	90–150
Timber rattler	40–90
Texas rattler	120–300
Florida rattler	240–450
B *South & Central American Species*	
Tropical rattlesnake	60–150
Fer-de lance	80–160
Bushmaster	300–500
C *Indian Species*	
Asiatic cobra	250–350
Russell s viper	200–300
D *African Species*	
Mamba	50–80
Puff adder	70–120
E *Australian Species*	
Tiger snake	35–50
Death adder	60–80

because of their wide distribution and because they represent the only poison ous species on some islands are two species of *Micropechis* occurring on Batanta New Guinea Jobi and the Solomon Islands Mueller s snake (*Pseudelaps muelleri*) of North Australia Ceram Mysol Salawati New Guinea Jobi and the Bismarck Islands and *Ogmodon vitianus* of the Fiji Islands According to our present knowledge these are not highly dangerous snakes but nevertheless are capable of inflicting a poisonous bite

Despite the fact that some of the important poisonous snakes of Australia possess a highly effective neurotoxic venom with reported mortality per centages as high as 10 and 50 per cent snake bite on this continent does not constitute a serious problem This is partly because of the scarce human population in rural districts the general inclination of the snakes to avoid man and the inferior biting apparatus of most species

Sea snakes have been omitted from this discussion on the geographical distribution of the important poisonous snakes Because of their habits their importance in the poisonous snake problem does not warrant further elaboration of the features mentioned previously

VENOM

Historical Note

The foundation for the modern study of snake venom was laid by Weir Mitchell between 1860 and 1896 This pioneer work was followed by the mas terful investigations of two French workers

Calmette in numerous publications described the properties and physiologic action of snake venoms and was the first to produce successful antivenin Much of his work was assembled in a summary publication in 1907 though further studies have been made since that date Dr Marie Phisalix critically evaluated and augmented the early investigations on venoms and a summary of much of her work was published in 19° in the two volumes entitled Animaux venimeux et venins This worker has continued her investigations up to the present time

These three workers are perhaps the outstanding pioneers in their field of investigation Their ranks have been amply augmented by investigators in practically all countries so that each year sees an increase in the contributions to our knowledge of the subject It is beyond the scope of the present account to list even the outstanding recent contributions but the reader is referred to the summary reports of Noguchi Brazil do Amaral Pawlowsky Maass and to the papers listed at the end of this article

Characteristics of Venom

Venom is a secretion of the supralabial glands situated on each side of the head behind the orbit These glands correspond to the parotid salivary glands of mammals and vary in size with the size and species of the snake The glands are surrounded by a fibrous capsule and receive fibers from the temporal

Neurotoxins affect particularly the respiratory center of the medulla or through spinal involvement the voluntary muscles of the body Venoms which are notably strong in this respect are those of the black snake of Australia (*Pseudechis porphyriacus*) the tiger snake of Australia (*Notechis scutatus*) and the death adder (*Acanthophis antarcticus*) of Australia and New Guinea the common krait (*Bungarus candidus*) of southern Asia and the Asiatic cobra (*Naja naja*) The venom of the tropical rattlesnakes is unusual among that of the pit vipers in that it is predominantly neurotoxic The neurotoxin of the South American rattler typically impairs the visual function of its victim in addition to its effect on the respiratory system The Central American rattlesnake has a strong neurotoxin which has a marked effect on voluntary muscles especially those of the neck Because of this natives believe that the bite of this snake breaks the neck of the victim

Cytolysins and *proteolysins* produce their effects through the destruction of cells thus causing local pain swelling necrosis and sloughing of the tissues followed often by gangrene The cytolysins are a complex group with extensive effects Russell s viper (*Vipera russellii*) of southern Asia possesses a highly cytolytic venom while the proteolytic effect is pronounced in the venoms of the bushmaster (*Lachesis muta*) the copperhead and water moccasin of the genus *Agkistrodon* and the Florida diamond back rattlesnake (*Crotalus adamanteus*)

Hemolysins and *hemorrhagins* are similar to the two preceding principles the hemolysin causes extensive destruction of erythrocytes with resulting anemia and respiratory disturbances and the hemorrhagin acts upon the capillary endothelium In general the venom of the VIPERIDAE and CROTALIDAE is characteristically strong in these elements while that of the ELAPIDAE is relatively weak in this respect However the venoms of the black snake of Australia (*Pseudechis porphyriacus*) and of the Egyptian cobra (*Naja haje*) have marked hemolytic effects

Hemocoagulins are present in two antagonistic types coagulant and anticoagulant Venoms are often well marked in the physiologic effects produced by these two principles It is generally thought that the poison of most VIPERIDAE and CROTALIDAE produces a more accentuated coagulation than that of the ELAPIDAE which often produces an anticoagulant reaction However the evidence at hand suggests that a number of exceptions cross the boundaries erected by this generalization

On the basis of the predominance of these elements venoms for practical purposes are classified into two general groups the neurotoxic and the hematoxic The neurotoxic venom is characterized by the action of strong neurotoxins and it is frequently anticoagulant Hematoxic venom is characterized by the strong action of cytolysins proteolysins hemolysins and hemorrhagins and is generally blood coagulant Because of the varying amounts and nature of these elements in venoms the two groups are not entirely distinct so that certain venoms contain marked properties of both types In general the VIPERIDAE and CROTALIDAE have a predominantly hematoxic venom while the

Chemical Characteristics

The fresh venom is a yellowish or sometimes colorless liquid of fairly thick consistency It is neutral or slightly acid slightly heavier than water and odorless It loses its toxicity after a short period if kept in the liquid state but it can be dried and kept indefinitely without losing its poisonous qualities When dried it becomes crystalloid but is readily soluble in dilute salt solution or distilled water Certain reagents such as nitrate of silver caustic soda potassium permanganate and gold chloride are able to destroy the toxic powers of the venom Ultraviolet rays and heat also destroy the toxic properties

The chemical complexity of snake venom is such that to date complete detailed analysis has been possible only in a few cases Much of the present information on venoms is contradictory and obscured through confusion Fortunately the work of investigators during the last decade is rapidly correcting this situation The study of venoms is a relatively new field of investigation offering promising results to the diligent but patient investigator

Substances of the following categories have been identified

1 Proteins (albumin globulin)

2 Lipoproteins

3 Proteoses and peptones

4 Mucin and related substances

5 Enzymes or ferments which cause most of the symptoms of poisoning

6 Epithelial detritus

7 Micro-organisms which are found only occasionally and usually not at all in purified venoms

8 Salts including calcium chloride and calcium magnesium and ammonium phosphates

Among these substances are found the various toxic constituents or antigens Not only do the venoms of different species of snakes differ in the proportionate amounts of these constituents but the various constituents also differ in the effects produced and in the immunologic aspects For example Githens and Wolff (1939) found that in the venom of North American pit vipers there are apparently two distinct neurotoxic constituents One of these which is presumably present in the venoms of all the North American pit vipers causes an early paralysis and acts largely on the respiratory apparatus The other causes a late paralysis and acts on the voluntary muscles of the entire body This latter constituent is more toxic than the former and is found in only a few of the pit vipers Further it has been repeatedly shown that there is no antigenic relationship between the neurotoxin of the ELAPIDAE and that of the CROTALIDAE and VIPERIDAE though the neurotoxins of the latter two families are somewhat related.

Venoms may be considered as mixtures of toxic constituents which are similar in their general effects but differ in certain forms in their specific effects and antigenic nature Among the most important of these toxic constituents are the following

symptoms produced by the neurotoxin may be muscular weakness ataxia and paralysis These are soon followed by symptoms of bulbar paralysis with difficulty of speech and swallowing as well as by facial and ocular palsy Respiration becomes weaker and weaker and is accompanied by cyanosis Death generally occurs from respiratory failure and may take place within an hour or not until three to six days after the bite If the quantity of venom is small general symptoms disappear rapidly and recovery is uncomplicated

It must be emphasized that the venoms of different snakes vary in respect to their toxic principles and consequently in their effects Unfortunately these statements about snake bite symptoms are of necessity only generalities At present no hard and fast rules can be given

DIAGNOSIS

The diagnosis of snake poisoning is usually simple because of the history and symptomatology However it must be remembered that in the case of certain of the ELAPIDAE symptoms may not be apparent for some time after the bite The time intervals between the bite and the onset of symptoms and between the bite and the victim s appearance for treatment are of the utmost importance The rapid onset of symptoms indicates a serious prognosis and a delay before treatment is an indication for strenuous therapy with less hope of a favorable outcome The type of snake involved must be ascertained Therefore the snake should be killed and brought to the physician for identification

Careful examination of the wound may reveal the type of snake responsible for the bite This method is less practical than most accounts indicate and should not be relied on exclusively in determining whether the bite was inflicted by a venomous or a harmless species The wound however may be useful in indicating the approximate size of the snake responsible for the bite

PROGNOSIS

Accurate prognosis in all cases of poisonous snake bite is extremely important but it is difficult because of the incomplete information available in many cases It is here that a knowledge of the poisonous snakes in the locality is of great value Among the important variables affecting the final result in any given case are the quantity of venom injected the potency of the venom the size of the victim and the treatment received The quantity and potency of the venom have already been discussed The size of the victim is of importance since the serum of the affected individual is able to neutralize a certain amount of the toxin in proportion to its quantity Thus a child receiving the same amount of venom as an adult will be unable to counteract it as effectively and will require more vigorous treatment

TREATMENT

The most valuable means of neutralizing or counteracting the venom toxins is by means of antivenins These are prepared by the immunization of horses occasionally sheep and other animals against the purified venom of a certain

ELAPIDAE have a predominantly neurotoxic venom Two outstanding exceptions to this generalization are the tropical rattlesnakes (*Crotalus durissus terrificus* of South America and *Crotalus durissus durissus* of Central America) and the Gaboon viper (*Bitis gabonica*) of Africa These have powerful neurotoxins in their venoms

PATHOLOGY

There are relatively few reports of the specific pathology of snake venom poisoning The pathology of poisoning by hematoxic venom may be illustrated by an autopsy on a patient bitten by a South American pit viper and reported by Eichelbaum (1927) At the site of the fang puncture on the leg the tissues were necrotic while the entire leg was edematous and discolored and local hemorrhages were present in the skin The lungs were filled with bloody fluid and petechial hemorrhages were visible in the viscera and mucous membranes *Microscopic examination by Dr Mallory revealed extensive degeneration of the* capillary endothelium numerous hyaline thrombi of the visceral capillaries and much blood pigment in the kidney tubules The pathology shows the effect of proteolysins cytolysins hemolysins hemorrhagins and hemocoagulins

Fairley (1929) reported Kilvington s studies on the effects of neurotoxic tiger snake venom on the brain and spinal cord of rabbits because they showed that the stigmata of toxic degeneration were most evident in the cells surrounding the central canal of the cord The cellular changes consisted of chromatolysis with degeneration and disappearance of the Nissl granules loss of muscular outline and finally disappearance of the nucleus itself

SYMPTOMATOLOGY

Because of the variation in composition of different venoms in respect to the toxic principles the symptoms produced vary accordingly In the predominantly hematoxic venoms severe and immediate local reactions are produced with pronounced pain progressive swelling of the involved portion and regional lymph nodes extensive ecchymosis and hemorrhage at the site of the wound Local gangrene often follows with secondary infection which may result in mutilation of the bitten part Systemic symptoms usually appear within a few *hours* with nausea vomiting or occasional diarrhea Hemorrhages may occur through ocular buccal gastric intestinal and vesical mucosa Thirst may become extreme and symptoms of shock may be noted with clammy skin dragging pulse and low blood pressure Dyspnea may result from extensive hemolysis Fatal cases go on to collapse coma and death often in six to twelve hours Mild cases exhibit recovery from systemic symptoms in a day or two but the local pathologic condition clears up more slowly

In the predominantly neurotoxic venoms the local reactions may be completely lacking or may consist only of burning pain at the site of the wound and slight edema and congestion with little or no tissue destruction Systemic symptoms may *occur immediately* or after several hours These are marked by nausea faintness vomiting headache lethargy and drowsiness The first

A recent development in serum preparation which has greatly enhanced its usage is the Lyovac method used by the Mulford Biological Laboratories The concentrated serum globulin is put up in powder form so that it can be put in solution immediately preceding injection The rapidly lyophilized antivenin is dissolved in distilled water for the purpose of injection This new method has abolished the necessity of keeping the serum in a cool place to avoid spoiling This former necessity limited the availability of the serum in warmer regions The new Lyovac serum package contains the vacule of powdered serum a syringe containing 10 cc of distilled water for dissolving the serum a 1 cc ampule vial of normal horse serum (diluted 1 10) for testing and desensitizing and a small ampule of iodine for antiseptic purposes

Antivenins are generally administered subcutaneously or intramuscularly but in critical cases should be injected intravenously for greater speed and efficiency though this involves greater risk Needless to say administration should be preceded by the usual test for sensitivity to horse serum In cases with a marked local reaction it is well to inject part of the serum locally in order to minimize necrosis of tissues The antivenin is most effective when injected immediately after the bite but it should also be used in late cases

The dosage of antivenin is governed largely by the amount of venom the potency of the venom and the weight of the victim The effect of the venom in general is inversely proportional to the body weight requiring several times as much antivenin for a child as for an adult In serious cases resulting from the bite of large snakes or in cases in which treatment is initiated late 50 cc or more of the antivenin may be required

Authorities do not agree on certain minor details of snake bite treatment but the principal procedures are those outlined in the following paragraphs Elaboration of these points with additional details of snake bites will be found in Chapter LXVII

1 Kill and keep the snake responsible for the bite This is extremely important from the standpoint of the proper antivenin to be administered

2 Apply a tourniquet immediately above the site of the wound on the bitten limb to impede the venous flow Tighten the tourniquet until the pulse can barely be felt The circulation should not be cut off entirely for any great time as this may result in gangrene Consequently the tourniquet should be loosened about every fifteen minutes for a period of about a minute

3 Short deep incisions should be made over the site of the bite through the fang marks Multiple incisions in the area surrounding the bite may be desirable The incisions should be made with aseptic precautions and should be one-quarter to one half inch long and one-quarter inch deep Suction either with the mouth or with a mechanical device should be applied to the incisions The latter method is to be preferred but the mouth may be used with comparative safety providing there are no sores or breaks in the mucous membrane If this method is used the mouth should be rinsed with a dilute solution of potassium permanganate which destroys the toxic properties of the venom It must be emphasized however that potassium permanganate must not be used

species of snake or against the venoms of several snakes The serum thus pre pared is of value in combating the venom of the snake or snakes for which it was prepared The serum may be effective against other species as well but it is not of value for all bites It has been found that some venoms contain more group antigens than others Therefore a serum prepared against a venom with a large number of such antigens would offer greater protection than one pre pared against a venom containing a small number of such elements Some of these group antigens may be common to the venoms of snakes of different genera while absent in venoms of some closely related forms The results of comparative immunologic studies suggest that each venom contains a large number of antigenic fractions Certain of these are related in several venoms while those of other venoms differ

Because of the antigenic nature of the venoms polyvalent serums can be prepared to be used against the venoms of a number of antigenically related species Thus a single polyvalent serum is made for the bites of all pit vipers in the United States The venoms of all species are not used in the preparation of this serum but only representative venoms of the different antigenic groups found there This same serum however is of little value against the antigenically different serum of the tropical rattlesnake and a special serum is made for it

Until the beginning of the present war the institutions mentioned below were actively engaged in the preparation of antivenins The Mulford Labora tories at Glenolden Pennsylvania produce a polyvalent Nearctic Crotalidae serum for the venom of the North American pit vipers and a polyvalent Bothropic serum for the pit vipers of the genus *Bothrops* in Central and South America The Instituto do Butantan at São Paulo Brazil prepares four types of antivenins (*a*) a serum for the venom of the tropical rattlesnake (*Crotalus d terrificus*) (*b*) a polyvalent anti bothropic serum to counteract particularly the South American species of the genus *Bothrops* (*c*) a poly valent anti ophidic serum for both the tropical rattlesnake and the members of the genus *Bothrops* (*d*) a serum for the venom of South American coral snakes The South African Institute for Medical Research at Johannesburg South Africa produces a serum for the venom of the Cape cobra the mamba the ringhals and several species of African vipers The Pasteur Institute of Paris makes a number of polyvalent antivenins (*a*) for all African snakes (*b*) for the snakes of West and Equatorial Africa (*c*) for the cobras (genus *Naja*) of Egypt and India (*d*) for the poisonous snakes of Europe The Central Research Institute at Kasauli India produces a polyvalent serum for the venoms of the Asiatic cobra and Russell s viper The Pasteur Institute at Bangkok Siam pre pares serums for the venoms of certain Siamese and Indo Chinese snakes The Institute for Infectious Diseases of Tokyo produces an antivenin for the venom of the habu (*Trimeresurus flavoviridis*) of the Riu Kiu Islands The Com monwealth Serum Laboratories of Australia produce serum for the bites of the important ELAPIDAE of that continent These antivenins are usually available in 10 cc ampules or in 10 cc sealed sterile syringes which are compact and readily assembled for emergency use

into bushes or burrows In snake infested areas these precautions should be enforced at all times

For collective protection there is no simple means of eradicating poisonous snakes From a practical standpoint it should be remembered that snakes frequent the neighborhood of camps or settlements to feed on the rodents which may be plentiful in such places Efforts directed at reducing the rodent population will also result in a reduction of the snake population The grounds in the region of a camp should be well cleared so as to offer the least possible protection to both rodents and poisonous snakes

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in the incisions or injected into the victim as it does more harm than good since *it destroys the tissues Suction should be employed vigorously and as the swelling* spreads new incisions should be made near its edge and suction applied to these Suction should be continued for from five to fifteen hours depending on the seriousness of the symptoms The suction may be briefly interrupted with short rest periods during which time the incisions should be covered with cloth packs saturated with strong salt or Epsom salt solutions

Some authorities disagree as to the advisability of the cutting and sucking The disagreement seems to have arisen from the fact that certain investigators have had experience only with the effects of predominantly neurotoxic venoms A summary of these conflicting views indicates that cutting and sucking are highly effective against the local action of the strong hematoxins but are of little value against the powerful neurotoxins Experimenting on a dog with the venom of the western diamond back rattlesnake Jackson injected four lethal doses of the venom and by means of numerous cruciate incisions and vigorous suction he was able to recover sufficient venom to kill two dogs although the original animal lived It seems advisable to use incisions and vigorous suction in all cases of snake bite even though in some instances it may prove an unwarranted precaution Care should be taken to prevent secondary infections at the site of the incisions

4 If proper antivenin is available it should be injected intramuscularly or subcutaneously above the tourniquet Part of the serum may be injected into the area of the bite to help combat the local effects Antivenin should be given as soon after the bite as possible

5 Local applications except for a mild antiseptic or salt packs are not advisable The practice of rubbing crystals of permanganate into the wounds is specifically condemned because of the resulting necrosis of tissue Cauterization likewise is strongly condemned

6 Sedatives such as aspirin or morphine may be given to help relieve pain Strychnine aromatic ammonia and other general stimulants should be used in cases of collapse Alcoholics should not be administered in any instance

7 In all cases blood transfusions or infusions of large amounts of physiologic salt solution are of great value in bringing relief to the victim and frequently mean the difference between life and death

8 Throughout the entire treatment the victim should be kept quiet and be prevented from undergoing any exertion

PROPHYLAXIS

Analyses of snake bite cases by numerous investigations show that most bites are inflicted on the feet and legs (50 to 60 per cent) or on the arms and hands (40 to 45 per cent) Protection for the feet and legs can be provided by wearing leather boots or heavy shoes with leather puttees Bites on the hands can be avoided by looking carefully before placing the hands on rocks or ledges while climbing in gathering material from trash or wood piles or in reaching

CHAPTER LXVII

MANAGEMENT OF SNAKE BITE

DUDLEY JACKSON

THE AMERICAN INDIAN WAS PROBABLY THE FIRST TO TREAT the bite of North American snakes successfully He was used to the rattle snake the copperhead and the water moccasin How early he learned to stab or slash the wound with the dagger of the pita bush and to suck out the venom we do not know but the Texas Mexican and the pioneer ranchman applied this treatment more than a hundred years ago

SYMPTOMATOLOGY

Immediately following the bite of most poisonous snakes there is a prolonged stinging pain at the site of the puncture One or two small puncture wounds are present depending on whether the reptile made a firm strike with both fangs or a glancing one with only one fang hitting the mark Often a tiny drop of blood or of bloody serum is present at these points In a few minutes there is local swelling and a bluish discoloration from hemolysis In nervous or allergic patients shock may develop quickly and may be accompanied by chill nausea and vomiting In none of the cases treated by the writer has the shock been fatal in most instances it has been relieved within an hour

After the first shock symptoms have passed and some of the intense pain is relieved by suction the patient feels much better But this feeling of improvement breeds a false sense of security in both patient and physician A Texas diamond back rattlesnake for instance can discharge 250 mg of venom or even more in one bite After initial treatment consisting of opening the wounds and applying suction for an hour or so the swelling will spread and in from 15 to 36 hours the patient will go into quick shock and may die unless transfusions are given quickly and repeated as often as necessary This crisis comes earlier in a child and calls for much more vigorous treatment A child under eight years is in dire danger if bitten by a rattlesnake

ABSORPTION AND PATHOLOGY

The venom of the rattlesnake copperhead or water moccasin when injected experimentally into the thigh of a dog is observed to spread slowly through the

NOGUCHI H Snake Venoms Washington D C Carnegie Institution 1909
PAWLOWSKY E N Gifttiere und Ihre Giftigkeit Jena Gustav Fischer 1927
PHISALIX M Animaux Venimeux et Venins Paris Masson et Cie 19 2
POPE C H Snakes Alive and How They Live New York Viking Press 1937
SHAW G E SHEBBEARE E O and BARBER P E *J Bengal Nat Hist Soc* 1, 113 1942
STALEY F H Case report of Gaboon viper poisoning with recovery *Bull Antivenin Inst* 3 31 1929

removed and replaced a few inches higher New cuts should then be made entirely around the limb following the swelling If possible several suction cups (Fig 117) (as many as half a dozen if they are available) should be used

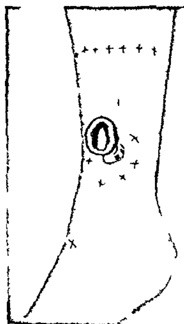


Fig 116



Fig 117

Fig 116 Incisions (cross cuts) neatly made nd plac d around the site of the b te and on edges of swell ng One suction cup n place (Ja kson *Amer c n Rifleman*)

Fig 117 Method of applying numerous suction cups in th treatment of a serious case of ake b te with marked swelling (*American Rifleman*)

and the suction should be maintained for from thirty to forty minutes out of each hour for about fifteen hours At the end of this time the physician may be able to withdraw larger amounts of blood tinged fluid If a small vein should be incised while the cuts are being made it should be plugged with a small piece of cotton and a new incision should be made nearby While resting the whole limb should be wrapped in heavy compresses which should be kept hot and very wet with a strong magnesium sulphate solution

4 At the discretion of the physician hypodermic injections of morphine may be given to relieve the intense pain

5 Because of the surgical nature of the treatment all cases of snake bite poisoning should be hospitalized if possible Several blood donors should be on hand for at least forty eight hours as the patient is likely to collapse suddenly

6 To replace the fluids lost by vomiting perspiration and suction the physician should administer from 500 to 1 000 cc of a 5 to 10 per cent glucose

intracellular lymph spaces into the lymph channels and finally into the vascular system Snake venom is too violent an irritant to be absorbed at once but as the lymph pours out and dilutes it it becomes more and more absorbable Hemolysis and some proteolysis are produced and great quantities of serum accumulate all of which contain the dilute venom as well as toxins from muscle and blood destruction Absorption takes place from the outer edges of the swelling If the venom is allowed to remain it is capable of hemolysis or proteolysis as well as destroying all tissue including bone tissue The course of this absorption can be traced beyond the swelling by the hyperemia and discoloration of the lymph glands above the swelling especially as it approaches the groin or axilla In late cases there is even a liquefying necrosis of the lymph glands which extends far into the abdomen and chest

These digested tissues make excellent culture media for bacteria so that gas gangrene is a common terminal complication In cultures made from the mouths of fifty captive snakes and one wild snake *Clostridium welchii* was found in every instance *Cl welchii* was also present in 50 per cent of the cultures made from the fresh wounds in snake bite patients

In dogs a bloody diarrhea is a not uncommon development before death Autopsy findings include ecchymoses of stomach and colon Little pathologic change may be noted in the small intestine Spleens observed were usually enlarged and occasionally livers were congested Anemia develops as death approaches and a count of 2 500 000 red blood cells is not uncommon Hemoglobin was as low as 35 per cent in one case

TREATMENT

There is plenty of time for careful treatment which should be promptly instituted

1 Place a light constricting band an inch above the wound

Make cross cuts (Fig 116) over each fang mark The skin should be sterilized and then quick firm cuts one quarter inch long should be made through the skin and across each fang mark

3 Apply light suction The earlier this is done the better The first few drops of bloody serum extracted are discouraging but they contain a strong solution of venom It is advisable to make all cuts deeper than necessary rather than to take the chance of failing to penetrate the skin Alternative suction on these two cuts should be kept up constantly for one hour This opening of the wound and the constant flow outward minimize the danger from *Cl welchii* and tetanus but it is not out of order to give an immunizing dose of these combined antisera

If antivenin is to be given this is a good time to inject it Three to five ampules are used locally and after one hour new cuts should be made Start suction again from these and from the original cuts This second row of cuts is made within an inch or two of the original wound following the edge of the swelling thus

As the swelling spreads upward the lightly constricting band should be

CHAPTER LXVIII

INSECTS AND OTHER ARTHROPODS INJURING MAN

C HOWARD CURRAN

INSECTS AND OTHER ARTHROPODS ARE OF CONSIDERABLE importance not only because they carry disease but also because some of them cause more or less severe illness as a result of their bites stings or other contact with human beings To be harmful to man an insect must be especially adapted to bite sting or bore into his body and only a relatively small number are so equipped

In the tropics the physician should learn what he can about insect pests from local inhabitants While it is true that few natives in tropical regions pay much attention to insects many of them are acquainted with those that cause bodily harm When they attribute injurious qualities to certain insects of terrifying appearance however they are usually mistaken because all large insects (not including large spiders and scorpions) are harmless It is among the small and inconspicuous creatures that the most dangerous ones are found

Although spiders ticks mites and centipedes are not insects they usually are included in studies of the relation of insects to disease because they are all arthropods—invertebrate animals with jointed legs

The several ways in which insects injure man directly may be summarized as follows

Biting Included in this group are only a small number of insects that have biting mouth parts the resulting injury being of a strictly mechanical nature The members of this group are not persistently predatory among human beings Some beetles may bite man occasionally but the chief offenders are ants Many tropical ants are vicious and persistent biters when disturbed The army ants of the American and African tropics will attack man in large numbers if he remains in their path

Sucking blood Most pests of man are blood suckers whose mouth parts have been modified for this purpose Despite this we generally refer to them as biting insects Mosquitoes and numerous other flies some bugs the sucking lice ticks mites and blood sucking fly maggots belong in this category

solution every few hours and from one to three blood transfusions are often necessary in severe cases These two measures cannot be too strongly stressed in a number of instances in which the patient has been in shock they have proved live saving

Cases of snake bite poisoning are seldom overtreated but deaths and near deaths have resulted from inadequate treatment The information obtained from repeated blood counts and blood pressure readings in addition to the rapidity of the swelling gives a good indication of the seriousness of the bite

Antivenin (Nearctic crotalidae) Polyvalent (North American Antisnake Serum) This serum is a valuable adjunct to the surgical or suction treatment of the North American snake bite It should not be relied upon to save the life of a seriously bitten patient Not less than five of the 15 cc ampules are injected into and around the area of the bite Another five ampules are injected subcutaneously into the arm thigh or abdomen Suction should be resumed one hour after the serum is injected locally The serum should be left for one hour in the tissues to neutralize locally all the venom possible

It is desirable to repeat the five ampule doses in three or four hours together with intravenous glucose and blood transfusions In patients who show a fall ing blood pressure weak pulse profuse perspiration and other symptoms of shock as many as fifteen ampules may be necessary to turn the tide

Common errors seen in treating snake bite

1 Failure of incisions to go through skin

2 Too few incisions (100 to 150 are often necessary) Too little suction

3 Lack of preparation for blood donors Early over confidence fatalities usually occur fifteen to forty eight hours after bite

4 Failure to recognize gas gangrene infection before it becomes widespread

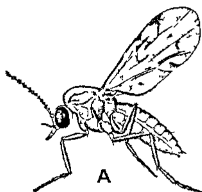
5 Following directions for small doses of antivenin recommended by manu facturers

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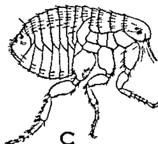
HARRISON W J and JACKSON D Mechanical treatment of experimental rattlesnake venom poisoning *J A M A* 90 1928 1928

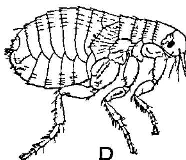
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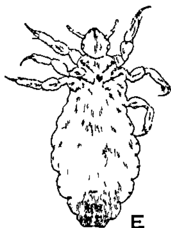
JACKSON D and CRIMMINS M L Treatment of snake bite *South M J* p 605 1 1 9











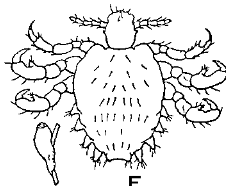


FIG 118 A Culicoides B Ornithodoros moubata C Rat fl a D Human flea E Body lou e F Crab lous and n t

Many normally harmless bugs that suck the juices of plants may suck blood or at least inject the proboscis for this purpose

Injecting poison Most of the blood sucking insects inject a poisonous substance into the victim when they bite This substance which is usually injected to increase the flow of blood to the seat of the bite varies considerably in different kinds of insects and may be mildly or highly toxic Spider venom is in some cases extremely toxic but it is injected into its victims normally other arthropods for the purpose of paralyzing them so that they may be eaten at leisure The same is true of the sting of the scorpion

Stinging Many HYMENOPTERA possess stings although male insects do not sting *These stings are modified ovipositors and are situated in the end* of the abdomen The poison injected is directly responsible for the injury The offenders are bees wasps and stinging ants The poison is normally used defensively (the honey bee) or for overcoming other creatures that are normally used for food by the insect or its larvae (solitary bees wasps and hornets) The scorpion sting differs entirely from that of insects Although used for the same purposes it is possessed by both sexes

Boring under the skin Some mites normally live just under the epidermis Scabies and mange are caused by this type of insect

Living intramuscularly The larvae of some flies normally live in this way notably the human bot fly and the Tumbu fly The larvae of some other flies may occasionally do so if they can gain access through wounds

Crawling over the body Insects may cause injury by crawling over the body if they are very numerous

Urticarial hairs The hairs and spines of larvae or adults or both of many kinds of moths are poisonous in some they are so constructed that they can work their way into the skin When the fine hairs are present in large numbers they may produce irritation The larvae of some butterflies also possess poisonous hairs

Carrying disease Transmission of disease by insects is either mechanical or cyclical In some instances the insect bites a healthy individual immediately after it has made an infective meal and the disease carried on the biting mouth parts is thus transmitted to another person Direct contact with infected sores or wounds followed by subsequent feeding on the skin of other individuals may directly carry the disease

MYIASIS

Myiasis is the term applied to infections caused by fly larvae The infection may be external or internal both types are found in the tropics Many cases of intestinal and intramuscular myiasis in human beings are accidental the result of attack by species of larvae that normally attack other animals Man is not a normal host for them In such cases contact with infested animals usually causes the transference of the eggs or newly hatched larvae to man In other cases flies deposit living maggots on open sores or rarely on mucous membranes

When there are several contiguous swellings there may be considerable sloughing and a gangrenous condition may develop

MAGGOTS

Congo Floor Maggot Auchmeromyia luteola is found in most of tropical Africa The eggs are laid in places where the larvae can find food particularly on sleeping mats crevices in huts and in sand They hatch in two or three days and the larvae feed at night when food is available but they are hardy and can exist for many days without food Hiding in cracks and crevices or under the surface of the ground during the day they come out at night and suck blood They may feed for as long as twenty minutes at a time

Symptoms Swellings appear on parts of the body in contact with the mattress or ground during sleep Often a light incrustation of blood covering the puncture follows feeding

FLEAS

Chigoe Flea The Chigoe flea *Tunga penetrans* should not be confused with the chigoe mites or chiggers (page 891) Although both are called by the same name they are very different creatures *Tunga penetrans* is found in America and Africa and is a serious pest It is often called sand flea but like many common names this name is applied to several kinds of insects and to other arthropods The female chigoe bores under the skin particularly of the feet but no part of the body is exempt from attack Between the toes the soles of the feet and beneath the toe nails are favorite points of entry into the body Before they burrow the Chigoe fleas may feed intermittently upon the host They are about 1 mm long but when the females are filled with eggs they may be the size of a pea The eggs are laid by the embedded female some falling to the ground while others hatch in the sore Most of the hatching larvae drop to the ground but some may develop to maturity in the wound

Symptoms The patient suffers from local and usually extreme irritation The area surrounding the flea is swollen and filled with pus When numerous the sores may become confluent and a most serious condition may develop culminating in the so-called auto amputation of toes often observed in West Africa The diagnosis may be verified by washing the wound thoroughly with warm water over a white dish and then straining the water through cheese cloth in order to obtain the female flea

Human Flea Pulex irritans is cosmopolitan in distribution It is very often called the sand flea It attacks human beings and many other mammals It is capable of carrying plague but is chiefly a pest because of its bite

BUGS

Bedbugs These insects are found everywhere They are not known to carry disease but many people are seriously affected by their bites Ordinarily the bites are less irritating than those of mosquitoes but large red swellings may

Ophthalmomyiasis Infection of the eye as a result of deposition of fly maggots is not common but numerous cases have been recorded during the past century In reported cases the victim has been unaware that infection has occurred until intense pain developed and vision became blurred There are usually *alternate periods of clear and blurred vision depending on the position* of the maggots Pain is intermittent occurring when the larva moves The maggot becomes visible only when it approaches the exposed surface of the eye Although they may remain in the eye for several weeks the maggots apparently do not develop to any appreciable extent They usually die while very small and are absorbed Blindness may or may not develop depending on the position of the larvae

The Human Bot Fly In tropical America from Mexico to southern Brazil the larvae of *Dermatobia hominis* Linne very frequently attack man The natural hosts are monkeys and large mammals The fly responsible for the infection is seldom if ever seen by the victim because it has the habit of catching other flies and laying its eggs upon them in positions that will not inconvenience the flight of the carrier

When the insect carrying the eggs comes in contact with a warm blooded body the eggs immediately hatch and the larvae adhere to the skin It was long believed that the bot larvae could not pierce unbroken skin but observations particularly those of Dr L H Dunn in Panama disprove this It is however probable that the larvae usually enter the body through the puncture made by the mosquito carrier Inasmuch as bot eggs are most frequently found on mosquitoes it seems probable that these are the natural carriers Unless killed or removed the maggots remain in the muscular tissue until fully grown when they make their way to the surface and drop to the ground to pupate

Symptoms During the first days of the attack there is swelling not unlike that caused by a mosquito bite or the sting of a bee and a week or two may pass before there is direct evidence of the presence of a maggot The presence of one or more mosquito bites that fail to subside may indicate infection by the human bot fly particularly if these occur on parts of the body which have been exposed After a time there are intermittent exudations from the center of the swelling and as time passes these increase in volume and frequency Later intense pains manifest themselves at irregular intervals and the maggot may indicate its presence when it moves from the muscular tissue to the surface to obtain air *At times the posterior end of the larva may be observed blocking* the entrance in the middle of the swelling As the larva nears maturity the swelling resembles a suppurative boil and blood is frequently mixed with the discharges

Tumbu Fly In Africa the larvae of several species of *Cordylobia* commonly attack man The flies lay their eggs in excrement polluted sand and soil the larvae hatching within a day or two If the larvae come in contact with the human body they bore through the skin

Symptoms Furuncular swellings appear in the case of isolated larvae and at times there is a discharge from the opening through which the maggot breathes

TREATMENT OF BITES BY BUGS

Wet compresses of sodium bicarbonate should be applied to the site of the bite Sedatives may be given if deemed advisable One to two teaspoonfuls of sodium bicarbonate in warm water may be administered internally

MITES

Many kinds of mites may attack man under certain conditions but few of them are serious pests Almost all the mites of domestic animals (particularly those of chickens and pigeons) and several kinds that feed on grain and cured meats will when they become extremely numerous bite man but they do not remain long upon him and a change of clothing usually takes care of the nuisance However some kinds of mites attack man rather persistently

Rat Mite The tropical rat mite (*Liponyssus bacoti*) is frequently a serious pest The adults are about 1 mm long but they are almost colorless Normally they attack rats and mice but if the rodents in a locality are destroyed they are likely to attack human beings Immature mites are very small and generally invisible so that their attack is generally attributed to some harmless insect It is very difficult to determine whether the patient is actually suffering from arthropod attack or is a victim of insect neurosis Small very irritating red swellings with tiny centers appear In early stages the attached colorless mite may be discerned in the center of the swelling under microscopic examination The victim scratches frequently and often causes painful sores and infection but true symptoms are obscure

Chiggers or Harvest Mites Other names are red bugs bete rouge and chiggoes They belong to the family TROMBIIDAE which includes the largest of the mites The chiggers that attack man are the larvae or nymphs which are microscopic in size The adults are relatively large velvety and red and may be seen frequently on tree trunks or crawling over the ground The eggs are laid on the ground and the tiny larvae crawl about on grass and weeds When a warm blooded animal comes along they attach themselves to it in much the same way as ticks do It has frequently been asserted that the chiggers bore into the pores but there is no evidence to support this The head is buried a poison is injected and edema in the form of hivelike swellings occurs The swelling surrounds the offending mite so that it appears to be buried Microscopic examination may show the mite in the center of the swelling Hivelike swellings may appear on any part of the body but particularly on areas where the clothing presses and in the crotch Extreme irritation and itching are present and may persist for a few days to a few weeks The fact that the patient walked through tall grass or weeds a few hours before infestation took place is suggestive of chiggers

TICKS

Ticks are common in almost all parts of the tropics In addition to carrying disease they may cause extreme irritation by their bites and they may cause

develop and may persist for several days The swellings are often accompanied by extreme local irritation

Triatoma Cone nose bugs of the genus *Triatoma* and some related genera

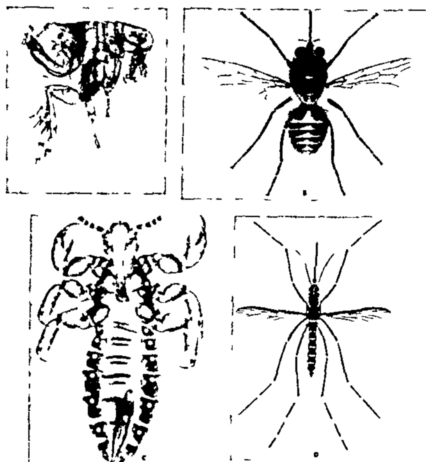


FIG 119 A *Xenopsylla cheopis* male rat flea Both sexes bite B *Glossina morsitans* carrier of sleeping sickness C Body louse male ventral view D *Aedes aegypti*

commonly bite human beings and they are capable of carrying certain diseases particularly Brazilian trypanosomiasis These insects belong to the family REDUVIIDAE (assassin bugs) a group that inflicts extremely painful bites One of them is known as the kissing bug because for some unknown reason it usually bites about the mouth of sleeping persons This species normally preys upon bedbugs and other insects and is generally beneficial

Symptoms In some cases symptoms may occur soon after the bite There may be flushed face palpitation of the heart rapid breathing and generalized urticaria The symptoms vary greatly in intensity and in many instances may be absent

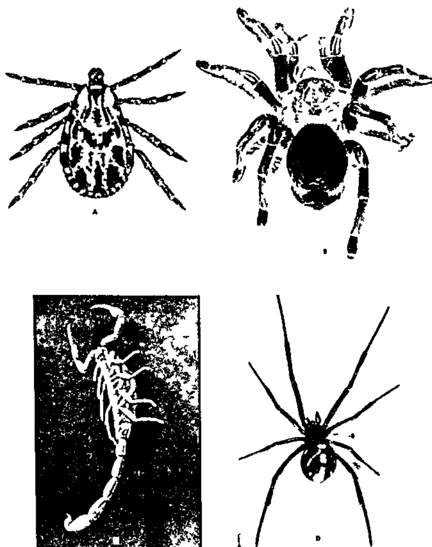


FIG 120 A *De   cento a d   n* typical of many of the dangerous ticks
B *Tara tul* Note that the palps (arro) are leglike There are about 500 ifferent T tie
C Scorpion—the palps a e clawl ke Most of the dang ous sp cies resemble this one
D Latrodect s—Bla k idow spider All pe es have markings similar to those shown in the illustratio

definite poisoning They may attach themselves to any part of the body but do so most frequently on the torso and lower part of the head very often about the nape of the neck and frequently in the ears Injury results when the tick attaches itself in order to feed because it injects a poison into the blood stream Gradually the whole capitulum of the tick becomes buried in the flesh so that the insect is held firmly in position by the strong barbs on its mouth parts Actually it is only the mouth parts that are embedded These are headlike and are termed the capitulum Unless removed the tick may remain attached from a few hours to a week or more depending on the kind of tick involved its body gradually distending until it becomes fully engorged The tick then drops to the ground and if it should be a mature female it soon lays eggs The ticks that cause most trouble to human beings belong to the genus *Ornithodoros* (*coriaceus talaje* and *turicata* in America and *moubata* in Africa) Numerous other species cause lesser trouble Some species inject poison into the blood stream and the results may be serious

Ornithodoros moubata The bite of this tick which is found in Africa is said to be very painful The wheals are large and raised Scratching increases the swelling which may cause discomfort for as much as a week after the bite occurs Immature forms of this tick also attack man and produce results as serious as those caused by the adults

Ornithodoros coriaceus The bite of the American tick may produce very serious and painful results and there are unconfirmed reports among the natives of loss of leg or arm Although these may be exaggerations it is possible that they may be true The ticks engorge in a relatively short time and drop off

Symptoms (O moubata and *coriaceus*) There is a reddish blotch one half to three quarters of an inch in diameter with bright red central spot later a discharge of clear lymph occurs and a red mottled scab forms Local swelling begins in about one hour and it is followed by more general and often extended swelling with extreme tenderness irritability and numbness The symptoms at least in part may be evident for several weeks If several bites are present the symptoms may be more severe and fever and nausea may be expected

In the case of tick paralysis in western North America resulting from the bite of *Dermacentor andersoni* there are no local symptoms but the patient becomes first lethargic then feverish and finally paralyzed The paralysis occurs a few days after the tick attaches itself and disappears completely a few days after it has been removed The species of *Dermacentor* cause no conspicuous local disturbance and they may remain unnoticed for days It is possible that paralysis may be produced by some tropical ticks

SPIDERS

Venomous Spiders Spiders sometimes bite man but most of the bites attributed to spiders are those of insects usually mosquitoes or other biting flies

TARANTULAS

Most of the large tropical bird spiders commonly called tarantulas are thought to be relatively harmless but the bites of some of them are definitely poisonous It is difficult to obtain any clear picture of the results of their bites because of conflicting statements and because the spider that does the biting may not be accurately identified In many cases it seems that the bite results in local swelling sometimes severe and aches and pains in the immediate vicinity often spreading to the whole arm or leg The bites of at least some of the American tarantulas are severe and although they do not produce the extreme suffering which results from the bite of the black widow similar symptoms and manifestations are present although in a milder form

Symptoms The symptoms noted are similar to those caused by the bite of the black widow but they are much milder and more likely to be localized Nausea dizziness and local numbness may be expected

Prevention No safeguards exist to protect people from the bites of tarantulas These spiders hide in dark places during the day consequently the hand or arm should be protected with a glove if it is necessary to probe such places

SCORPIONS

Scorpions are related to spiders but they do not bite they sting The poison bearing glands are situated in the tail the end of which is more or less bulbous with a tapering sting When the scorpion strikes the sting is thrown forward over the head Most scorpions inflict stings which are locally painful but not serious However there are many kinds that cause serious systemic disturbances The best known of the poisonous tropical scorpions are the Durango scorpion of Mexico and the two North African scorpions *Prionurus australis* and *Buthus occitanus* Deaths from scorpion stings are not infrequent

Symptoms Following the sting local numbness develops This gradually spreads and itching of the nose and throat excessive production of saliva and gradual collapse followed by waves of convulsions occur Recovery may be gradual or death may follow

CENTIPEDES

Centipedes are elongated flattened wormlike animals with a single pair of legs on each segment of the body The front pair of legs have been developed into poison fangs Some centipedes attain a length of 6 or 7 inches and these are greatly feared by many people They live on other animals chiefly worms insects and spiders Actually most of them are harmless The small ones are unable to pierce the skin with their fangs and those that can usually cause no worse symptoms than the bite of a mosquito However with neurotic people the bite may be the cause of systemic disturbances and some bites may cause local swelling pain and sometimes bleeding since the fangs may dig rather deeply With the largest ones a light bite causes only slight discomfort

However a small number of the thousands of different kinds of spiders may cause serious injury when they bite Spider bites can usually be distinguished from insect bites or stings by the presence of two approximate reddish punc tures produced by the palpi of the spider Occasionally only one palpus pierces the skin The size of the spider does not determine the severity of its bite Some large spiders commonly called tarantulas are not at all or are only slightly poisonous The black widow spiders are rather small but they are among the most dangerous although death rarely occurs as a direct result of their bite

Black Widow Spiders There are several species of *Latrodectus* and the genus occurs in most tropical and temperate regions All may be recognized by the presence of a reddish or yellowish hourglass shaped spot on the under side of the abdomen but in rare instances the spot is divided into two or still more rarely it is entirely absent Usually when the spot is reduced the anterior por tion remains as a more or less transverse oval band In the tropics the spot is variable both in the same species as well as in different species *Latrodectus* may be grayish yellow grayish brown or black and there is usually a dorsal pattern of a lighter color commonly of a yellowish tinge In some cases the light mark ings are a brilliant red in others they are almost whitish It is to be noted that no other spiders have the hourglass shaped marking and its presence identifies a spider as a species of *Latrodectus*

Symptoms Herms gives an admirable account of the symptoms and states that once recognized they cannot be confused with other diseases although *Latrodectus* poisoning has been variously diagnosed as ruptured gastric ulcer acute appendicitis renal colic tabetic crises tetanus and food poisoning

The symptoms make themselves apparent within about fifteen minutes after the bite occurs There is usually slight local swelling accompanied by pains which are likely to be intense There is definite leukocytosis but this is soon overcome by the venom which spreads in the blood stream and along the nerve cords Local numbness and rigidity of the muscles occur and these symptoms soon manifest themselves in the larger muscles of the body which may become boardlike Spasms occur The patient suffers from dizziness weakness of the legs and abdominal cramps and usually has difficulty in breathing Local or general rash may develop and the whole body usually becomes very sensitive The pulse may be weak In most cases there is heavy sweating early in the onset The most severe symptoms develop within one to three hours and may persist for as long as two days gradually subsiding after the peak has been reached Once the crisis has passed complete recovery usually occurs within a few days

Other Spiders In Australia there are two dangerous species of large spiders belonging to the genus *Atrax* These are related to the American tarantulas The effect of their bite is said to be practically the same as that of the black widow and the general treatment is the same

The bite of other spiders is little if any worse than the sting of a bee Local applications of hot compresses relieve the pain and itching

but if a considerable amount of poison is injected the results may be quite pronounced The only small species that has a bad reputation supported by reliable evidence is the house centipede a long legged species that inhabits dwellings where it feeds on bedbugs cockroaches and other insects The bite sometimes produces much local swelling and systemic disturbances of a mild nature

Symptoms As a rule the symptoms of centipede bites include local swelling about as in bee sting Under exceptional circumstances the swelling is accompanied by a rise in temperature extreme nervousness and rarely by slight nausea The two fangs may be pulled backward causing slight laceration or redness

URTICARIAL HAIRS

Large numbers of caterpillars and moths have hairs that possess stinging or other irritating qualities In many cases the hairs contain a poisonous substance but in others the irritation is caused by very fine or barbed hairs that work their way into the skin and cause painful sores Sailors in tropical ports at the time of the flight of certain kinds of moths often suffer from sore eyes sores about the mouth and between the fingers and at times on the neck and upper part of the body This frequently happens in South America where moths of the genus *Hylesia* are attracted to the ship s lights in large numbers The hairs are broken off as the moths fly about and are forced into the skin when touched by the fingers or eyelids They are held by the moisture about the mouth and eyes and when they settle between the neck and clothing they are forced by pressure into the skin A more direct method of infection is the result of handling the moths themselves

Most of the caterpillars of these moths as well as of many others have poisonous hairs or spines When these come in contact with the human skin the reaction is almost instantaneous resulting in intense irritation (like severe nettle stings) which often lasts for many hours In others the hairs cause injury as in the case of the moths

Symptoms The symptoms for which these urticarial hairs are responsible are irritation about the eyes and mouth a localized rash frequently with considerable swelling and occasionally edema The eyes may be closed by swelling of the lids In cases of larval contact local irritation and rash may be present

TREATMENT

General

Most people pay very little attention to the bites and stings of insects As a rule the edema or itching which may cause distress to susceptible individuals can be relieved by the application of hot compresses of a strong solution of sodium bicarbonate When the pain or itching has been alleviated the liquid should be allowed to dry on the body Applications should be repeated until complete relief is obtained Ether or alcohol may also be used to relieve the itching Specifically this is for treatment of irritation caused by mites

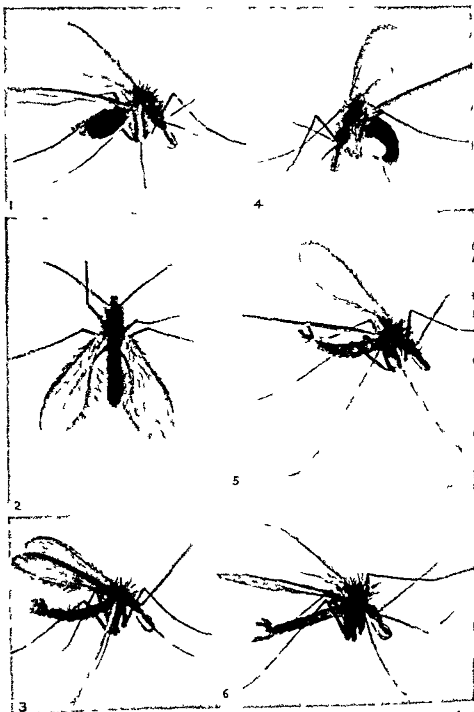


Fig 1 1 Three species of *Phlebotomus* 1 *P verrucarum* female engorged about two days previously *P verrucarum* female unfed 3 *P verrucarum* male 4 *P noguchi* female recently engorged A mite is attached to the abdomen 5 *P noguchi* male 6 *P peruensis* male (Hertig M Courtesy of the *American Journal of Tropical Medicine*)

the larva will then be unable to obtain air it suffocates and when the tape is removed after ten hours or more the maggot almost always adheres to it If the dead maggot does not come free with the tape a sharply curved or hooked needle may be used to remove it If this fails an incision must be made immediately as failure to remove the dead maggot at once may result in infection Maggots inadvertently killed during sleep or ignorance of their presence may cause great suffering and recovery may be slow

When there are numerous swellings due to fly larvae there may be considerable sloughing and wide incision and curettement may be necessary

In cases of ophthalmomyiasis pain should be relieved Further treatment must be governed by the development of the maggot and upon the amount of tissue destroyed Removal of the eye is not indicated unless other symptoms such as collapse of the eyeball develop

PREVENTION

The prevention of insect attacks is dependent on their habits but there are certain methods which are applicable in most instances As a general rule beds should be raised from the ground and the feet set in tins containing kerosene or water If raised beds are not available clean sleeping mats may be placed on uninfested ground Both the mats and ground should be sterilized This can be accomplished by spraying with kerosene containing rotenone or pyrethrum It is important that all cracks and crevices be thoroughly treated The ground may be sterilized by raking and mixing in a small amount of arsenic or fluoride powder in the proportion of about 5 ounces to 10 square feet Spraying the ground or floor with the kerosene mixture mentioned is of value Kerosene alone is of value for beds mattresses and walls but in order to effect satisfactory control especially of bedbugs weekly applications must be made Cyanide fumigation if sufficiently concentrated will kill both bugs and eggs but it should be carried out only by an experienced operator The elimination of all rodents together with careful spraying with one of the usual fly sprays or the kerosene mixture mentioned above is important especially for the elimination of rat mites The addition of cinnamic aldehyde (1 ounce per gallon) increases the repellent qualities of the spray

The prevention of ticks and mites is of great importance Ticks generally inhabit grasslands and low foliage and are rarely found more than a few feet from the ground Many tropical seed ticks occur on the trunks of trees probably lying in wait for climbing mammals Since most ticks live near the ground they usually make contact with the legs or feet of human beings Ticks almost always climb upward Most tick bites can be prevented if proper clothing is worn that is with the socks outside the trousers and the shirt inside the trousers In this way the ticks are forced to climb to the neck in order to come in contact with the body and since this contact occurs in a sensitive region they may be easily detected and removed before they have time to become attached

No satisfactory means of tick control has yet been developed In the case of tick infested dwellings the buildings should be thoroughly cleaned and if

In all cases in which insect bites or stings cause undue suffering sodium bicarbonate or other alkaline material should be given internally Hot or cold compresses depending on the patient s reaction should be applied Ice packs or hot water bottles may also be used

Scorpions and spiders

Treatment of the bites of spiders is varied Three treatments which are now generally recommended are

1 Use of *Latrodectus* (black widow spider) antivenom according to the directions on the package (Mulford Laboratories Philadelphia)

2 Intravenous injection of Epsom salts

3 Magnesium citrate taken internally

In the treatment of the bites of both spiders and scorpions it is most important that the patient should obtain complete rest and that sleep should not be interrupted The internal use of alkaline solutions is recommended and sedatives should be administered Hot baths give relief and sweating should be stimulated For the treatment of scorpion bites scorpion antivenom should be administered when available according to the directions on the package

In the case of tarantula bites for which there is no antivenom an incision should be made at the site of the bite and the wound allowed to bleed freely Such action should be taken only within an hour or two after the bite occurs After this time the poison will have passed into the blood stream so that this treatment will have no beneficial effects Ice packs or cold compresses should be applied immediately to reduce the flow of blood to and from the area After a lapse of two or three hours hot compresses should be employed to reduce local irritation

For the chigoe flea turpentine iodine chloroform or potassium permanganate should be applied to kill the flea All suppurative matter should be removed and the wound sterilized again

Ticks

The first step in the treatment of tick bite is the removal of the tick This must always be done with great care as the head may become detached from the body and remain in the wound The ticks may often be induced to detach themselves by touching them with a hot needle by applying a very hot compress or by dropping on them a small amount of alcohol ether or chloroform If these methods prove inadequate or are not practicable the body of the tick should be firmly grasped with a pair of tweezers and a gentle but steady pull exerted Should the head become separated from the body surgical removal is indicated

Fly Larvae

In infection with fly larvae it should be noted that the larva breathes through the surface opening and it is usually possible to bring it to the surface by plugging the hole This may be done with waterproof adhesive or scotch tape but if neither of these is available chewing gum may be used As

CHAPTER LXIX

THE RECOGNITION OF INSECTS AND OTHER ARTHROPODS CARRYING DISEASE OR INJURING MAN

C HOWARD CURRAN

MOST OF THE INJURIOUS INSECTS AND THEIR RELATIVES belong to groups which can be fairly easily recognized even without much technical knowledge of the terms used in classification

The following classification is based on characteristics which are easily seen although magnification of × 10 or more may be necessary

A ARTHROPODS WITH NUMEROUS ABDOMINAL SEGMENTS AND ONE PAIR OF LEGS TO EACH SEGMENT

The only venomous arthropods which fall under this heading are centipedes They are flattened dorsoventrally and the legs arise from near the sides of the segments (Millipedes have two pairs of legs to each segment and are strongly convex above They live on vegetable matter and secrete a fluid which is objectionable to some people Certain land inhabiting Crustaceae have five pairs of legs and curl up when disturbed They also live on vegetable matter)

B ARTHROPODS WITH FOUR PAIRS OF LEGS BUT OFTEN WITH A PAIR OF LEGLIKE PALPS (CATERPILLARS HAVE THREE PAIRS OF TRUE LEGS AND TWO OR MORE PAIRS OF FALSE ONES)

Scorpions The scorpions have four pairs of legs and a pair of chelicerate palps somewhat resembling the front legs of a crab The tail is composed of narrowed abdominal segments and ends in a sting which is more or less bulbous at the base The scorpion shown in Figure 1 0 is typical of the poisonous forms

Spiders These are distinguished from their relatives by the presence of four pairs of legs a pair of palps that may be leglike and by the structure of the head and thorax which are firmly united and appear as one piece whereas the abdomen is freely articulate and composed of a single unit A distinct waist separates thorax and abdomen a character not found in ticks mites

possible scrubbed with strong soap and water If live steam is available it should be directed into cracks and crevices in the floor and walls Spraying with a strong solution of nicotine sulfate or kerosene containing cinnamic aldehyde is of value Arsenical dusts also help prevent the development of young ticks especially in chicken yards One ounce raked into every ten square feet of ground should prove sufficient

Dusting of sulfur powder under the clothing before going into chigger infested areas is said to be of great value Sulfur may be taken internally When administered in this way the sulfur is given off through the pores and thus prevents chigger attack In the event of any ill effects the drug may be temporarily discontinued and one half the amount used when the treatment is resumed after a week or two In the case of those who cannot change their clothing frequently the sulfur saturates the clothes so that the daily internal dosage may be discontinued after three or four days Although this form of sulfur prevention has not been fully tested it has been successful in a number of instances

Practically all tick bites can be prevented by daily examination of the body Inasmuch as ticks seldom attach themselves to the body for several hours after reaching it an examination every day after returning from the field will prevent serious bites as well as disease from infection Even after a tick has become attached it may be several hours before it can transmit disease or inject sufficient poison into the body to cause inconvenience Ticks attached to the back of the head may be discovered by rubbing the hand over the hair If lumps are found the area should be critically examined

Lathering the body with mild soap or shaving cream has been suggested for the prevention of chiggers The grease possibly prevents chiggers from obtaining a firm foothold on the body It is necessary to be cautious however because of the danger of clogging the pores if used continuously

Spiders like scorpions hide in dark places during the day and come out at night in search of food The spiders build their webs in darkened corners or among rubble and adjacent to stones Because of these habits most of the bites occur on the hands and in the region of the genitalia as a result of sitting on outdoor toilets beneath the seat of which the spider has built its web All black widow spiders should be killed and webs on outdoor privies should be removed Since most spiders are beneficial no general extermination of them should be undertaken

In regions where scorpions are numerous about buildings or tents clothing and shoes should be carefully examined before they are put on Mosquito netting will keep scorpions out of beds but hands or arms should never be put into dark places unless protected by gloves

The house centipede usually bites sleeping persons so that the destruction of any centipedes that may be observed is the only preventive measure of value

Entrance of moths can be prevented by screening Cheesecloth screens may be used to prevent the entry of scales

these can be recognized only by experience All smooth caterpillars are harmless

Fleas Fleas may be recognized because they are laterally compressed are of leathery structure and hop Figure 118 shows the characteristic shape of fleas from the side The various kinds are not easily separated but all fleas may be suspected as disease carriers and almost all of them will bite human beings when hungry

Bugs A number of wingless bugs will bite human beings but the *bedbugs* are of characteristic shape They have a peculiar odor (shared by some related winged genera) which aid greatly in their identification When the bug is crushed between the fingers the odor is pronounced and easily recognized Like fleas they have tubular sucking mouth parts Other consistently biting bugs are winged

Lice The lice that attack man are the sucking lice Their mouth parts are adapted for sucking blood They are flattened dorsoventrally and are of a soft texture They should be easily recognized by comparison with Figure 118

D ADULT INSECTS HAVING ONLY ONE PAIR OF WINGS FLIES

In the broad sense the DIPTERA or two winged insects are all flies but these are divided into a number of groups not only scientifically but in the public mind as well In general the public recognizes three groups mosquitoes midges and flies

The mosquitoes may be recognized by the long sucking proboscis and the presence of scalelike hairs on the wings They are moderately fragile and have long slender legs There are other flies with longer legs but they lack the scales on the wings and even though some of these may have a long proboscis they do not bite

The midges are generally more delicate than mosquitoes they lack the scales on the wings and even those that bite (some very small ones) have rather short mouth parts Some of the larger midges are often mistaken for mosquitoes but since they do not hum and are not attracted to people they are soon recognized as harmless

Flies is a general term applied to the more robust members of the DIPTERA regardless of size The term is perhaps best exemplified by the housefly green and blue bottle flies in houses and the deer and horse flies that attack people out of doors There are many thousands of different kinds of flies but only a relatively small number of them bite

There is no doubt that the DIPTERA are the most important vectors of disease among the arthropods and that most of the biting pests belong to this group of insects

Mosquitoes The mosquitoes are divided into two main groups both of which are important (A third group is often included in which the mosquitoes lack scales on the wing veins and body they are not blood suckers) There are disease carriers in both the Anopheline and Culicine groups the former being well known because they transmit malaria the latter because of their con

and harvesters (daddy long legs) Even newborn spiders have four pairs of legs

Black Widow Spiders These are the most easily recognized of all the spiders All have normally the hourglass shaped marking on the under side of the abdomen No other spider has this marking The general color may vary from creamy white to shining black There may or may not be lighter colored markings on the upper side of the abdomen The hourglass marking may vary from almost white through yellow to brilliant red and the same is true of the dorsal markings The male is much smaller than the female and has a much more elongated abdomen The adult female abdomen is almost orbicular Figure 120 shows an immature female The following are some of the local names Cul rouge (Santo Domingo) mico (Bolivia) lucacha (Peru) arana capulina (Mexico) malmignatte (Southern Europe) katigo (New Zealand) and knoppie spider (South Africa)

Tarantulas These are large hairy tropical or semitropical spiders All appear to have five pairs of legs the palps being long and leglike All are dangerous looking and some of them are poisonous The true classical tarantula of Europe is a moderately small long legged spider the bite of which is at most mildly poisonous and not at all dangerous Because of the belief in the deadliness of the European tarantula bite all large dangerous-looking spiders have been called tarantulas It is not possible to differentiate between the dangerously poisonous and slightly poisonous tarantulas and too little is known about them to recognize which are and which are not poisonous

Ticks and Mites The abdomen and thorax of ticks and mites are joined in their full width so that there is no waist The mouth parts represent the head which is not truly differentiated from the thorax The immature stages have only three pairs of legs agreeing in this respect with insects All stages of insects that have three pairs of legs have a distinct head although many of those that lack legs have no distinct head

Ticks When unengorged the tick is a flattened leathery creature but when it is filled with blood it is more or less bean shaped The palpi of ticks are elongated and jointed Ticks of the genus *Ornithodoros* have not the smooth leathery appearance of most ticks but usually have an irregularly grooved body Both kinds are shown in the figures

Mites These are mostly soft bodied and do not expand noticeably when filled with blood Those which attack human beings are tiny microscopic animals while ticks are larger and always easily visible to the naked eye

C ARTHROPODS WITH ONLY THREE PAIRS OF TRUE LEGS AND WITHOUT WINGS

These are insects Some are extremely small but all that attack human beings are visible to the naked eye

Caterpillars The caterpillars causing injury because they bear barbed or poisonous hairs are easily separated from mature insects because the former bear in addition to the three pairs of true (tapering) legs in front five pairs of false stumpy legs Numerous caterpillars may be classed as urticarian but

typical of the genus the antennae are composed of three segments the third elongate and bearing a loosely plumose arista

Glossina There are very few species of tsetse flies and all occur in Africa The tsetse flies are brownish or grayish and reddish and are dull and unattractive in appearance Among the African flies they may be easily distinguished by the long proboscis wing venation and plumose arista Some species of *Stomoxys* (stable flies) somewhat resemble them The proboscis of *Stomoxys* is long but the wing venation is different The species of *Glossina* are not easily separated from each other by the amateur They are found along rivers the edges of forests and sometimes on wooded plains The larvae develop to maturity within the female fly

Cordylobia and *Auchmeromyia* These two African genera are not biting flies The mouth parts are greatly reduced the proboscis very small A number of African flies have the same characteristics The larvae do the damage but these are not easily differentiated from other fly maggots

E INSECTS WITH FOUR WINGS (THREE PAIRS OF LEGS)

Reduviid Bugs Triatoma and a few other assassin bugs bite and some carry disease They have sucking mouth parts that curve backward under the thorax and rest between the legs the base of the mouth parts project strongly forward (when viewed from above) while in almost all the non blood sucking species it scarcely projects The sides of the abdomen are thin and distinctly upcurved usually checkered reddish or yellowish and black the wings lie flat over the depression of the upper surface of the abdomen the legs are rather long and slender

Moths The moths have large membranous wings that are covered with scales which produce the color patterns The mouth parts except when greatly reduced as in the non feeding adults are coiled like the spring of a clock The antennae are never clubbed at the end but are usually plumose The moths possessing stinging hairs are variable in size shape and color so that it is impossible to give characters by which they may be recognized

F FLY MAGGOTS—LEGLESS AND TAPERING TO THE MOUTH

The larvae of flies are of various forms However those attacking man belong to the family METOPIIDAE and those belonging to this family are fairly easily recognized In the group of flies to which they belong (the *Muscoids* or *Calypterae*) the larvae are mostly of the same general type They are legless segmented tapering to a point in front and more or less truncate behind In related families the posterior spiracles (breathing tubes) are either flush with the surface or project beyond it In the *Metopiidae* the spiracles are situated in a fairly deep cavity and are flush with the surface of the cavity so that they are visible only when the larva is examined from behind This cavity can be closed by the larva thus imprisoning air which can be breathed when the larvae enter liquid media as most of the carcass feeding kinds do The larvae of *Cordylobia* and *Auchmeromyia* have this cavity and this together with their habitat serves to identify them

nection with yellow fever Other diseases are transmitted by members of each group

Anopheles The Anopheline mosquito is readily distinguished from other adult mosquitoes because its scutellum is almost evenly convex apically the abdomen is usually without scales or they are rather few in number When this mosquito is at rest the body is held at an angle of about 45 degrees Its wings are almost always spotted The eggs are found singly or in loose masses on the water and have characteristic floats The larvae are surface feeders and rest with their bodies parallel with the surface of the water

Culex Aedes and other Culicines The scutellum of the mosquitoes belonging to this group is concave toward either side so that it is trilobed and the abdomen is wholly covered with scales When these mosquitoes rest the abdomen is parallel to the surface and the wings are rarely spotted The eggs may be laid singly in loose masses or in compact floats The larvae rest at an angle to the surface of the water

Culicoides The *Culicoides* are very small biting midges They are commonly called punkies no see ums and biting midges The wings usually are variegated grayish and lighter color and the pale markings are sometimes whitish The body color varies from pale yellowish to blackish The gray color of the wings is due to the presence of patches of black or brown hairs the color of the patches depending often on the density of the hairs The antennae are elongated Specific identification is very difficult Several tropical species carry disease

Phlebotomus They are psychodids and are related to the common moth flies a group in which the wings are angularly bent near their base so that the two together are rooflike They are very small flies with grayish tinged wings all the veins on the upper and lower surfaces and the borders of the wings bear rather long hairs Their small size arrangement of the hairs on the veins the apically rounded wings and elongated antennae aid in their recognition Many other flies have hairs on the wings but they are either very short much restricted or scattered over the membrane Some *Chaoboridae* closely resembling mosquitoes approach this description but they will be readily distinguished by their longer legs and larger size

Simuliidae The black flies may be recognized by their compact form delicate shining broad wings with strong veins in front only They vary considerably in size and the color ranges from rusty yellowish to velvety black

Chrysops These are commonly called deer flies and there are many species of them The antennae are composed of three segments the third of which is long and annulated but the annulations are not articulated Most of the species resemble each other but there is great variation in the color of the wings and body

Musca domestica The housefly occurs over most of the world but is replaced in parts of the old world tropics by other species of *Musca* The abdomen varies in color being sometimes mostly yellowish at other times with very little red on the sides toward the base The wing venation and shape of the head are

SECTION ELEVEN

EFFECTS OF HEAT HYGIENE AND SANITATION

CHAPTER LXX

HEAT PROSTRATION

Z T BERCOVITZ

THOSE WHO ARE NOT ACCUSTOMED TO THE INTENSE HEAT of the tropics may be seriously affected by it when they have to live in tropical countries Exposure to such heat may lead to heat exhaustion heat pyrexia or to heat cramps It is generally believed that people suffering from impaired function of the kidneys heart and thyroid should avoid living in the tropics

HEAT EXHAUSTION

Heat exhaustion is seen in heat prostration or heat syncope It is characterized by prostration circulatory disorders but little if any rise in temperature There is a sudden onset of weakness nausea headache giddiness and staggering The temperature may rise to 100 or 102 F but usually there is no such initial rise in temperature The blood pressure falls rapidly the pulse becomes small weak and rapid and the skin is cold and clammy

Most cases of heat exhaustion recover with rest alone but in some instances the condition is fatal General supportive treatment and rest are indicated for these patients Drafts are to be avoided but the patient s clothing should be loosened and he should be placed where he can get plenty of fresh air and quiet If his temperature is subnormal he should be wrapped in blankets and hot water bottles may be put at his feet Caffeine is a good stimulant

HEAT PYREXIA

Heat pyrexia is also known as thermic fever heat hyperpyrexia heat stroke sun stroke sun traumatism and siriasis It is characterized by high fever and severe symptoms that are caused by exposure to excessive heat high humidity and absence of movement of air When exposed to such conditions the body fails to eliminate the excess of heat Strenuous physical exercise heavy or tight clothing that does not allow free circulation of air alcoholic beverages and debilitating diseases are the main etiologic factors involved Cessation of perspiration frequently comes before an attack and this may be related to failure on the part of the patient to take sufficient water

HEAT CRAMPS

Heat cramps (miner s cramps stoker s cramps fireman s cramps etc.) are painful spasms of the muscles following muscular exertion at high tempera tures Deficiency of sodium and chloride is apparently the chief causative factor for it has been found that sodium chloride is excreted in the sweat of individuals who have not been acclimatized or who are not accustomed to hard physical work in high temperatures

Heat cramps usually occur in the extremities they may be transitory but may recur at longer or shorter intervals Moderately severe heat cramps are very painful and may disable the sufferer The distribution of the cramps is symmetrical As a rule the onset is gradual The cramps increase in severity as the condition progresses

Treatment of heat cramps involves rest and restoration of the sodium chloride content of the blood and also of body fluids To this end intravenous infu sions of sodium chloride with 5 per cent glucose should be given Sodium chloride tablets taken by mouth are also of value

Prophylaxis involves the maintenance of body nutrition with a well rounded diet adequate fluids and salt It has been estimated that 1 gm of sodium chloride daily is necessary for those engaged in hard labor in hot weather The liberal ingestion of salt is of greatest importance

The sudden onset of symptoms is usually preceded by a forty eight hour period in which the patient does not sweat Then muscular weakness head ache vertigo anorexia thirst and slight increase in body temperature and in pulse rate appear and these in turn are followed by high fever The tempera ture may reach 105° to 110 F and it is associated with delirium cyanosis and coma Nausea and vomiting may occur but the important symptoms to watch for include convulsions with the vomiting photophobia suffusion of the eyes and irritability of the bladder In severe cases death may take place in a very short time Cheyne Stokes breathing or irregularity of breathing must be re garded as grave prognostic signs The pupils may be contracted until the terminal stages when they become dilated The pulse is full and bounding at first but later it becomes feeble small rapid and irregular Cyanosis and clammy skin are late symptoms Heat cramps may develop as a result of salt depletion Recovery is usually marked by a fall of temperature presence of diuresis improvement of pulse The patient begins to sleep quietly Sweating is a favorable sign

Bronchopneumonia which may result from pulmonary congestion is a com mon complication When moderate fever persists some intercurrent infection should be suspected Headache photophobia and giddiness may persist for weeks

In making a diagnosis the physician should bear in mind all other causes of fever for patients in the tropics may have malaria enteric fevers or pneumonia

Prognosis depends on the severity of the symptoms and the promptness and thoroughness of the treatment as well as on the age and vitality of the pa tient and on the presence or absence of complications Alcoholism and cardio renal disease predispose to poor prognosis

The treatment of heat pyrexia includes absolute rest rapid reduction of the temperature replacement of fluids and cardiac and circulatory stimula tion The patient should be placed in the coolest place available he should be covered and packed in ice if possible and should be given colonic irrigations of ice water He may be wrapped in a sheet that is sprayed with cold water During treatment the patient must be watched carefully for collapse or for a too rapid drop in temperature When the temperature has reached 10 or 103° F the treatment should be stopped and the patient should be allowed to rest in a light dry blanket According to Marsh (quoted by Strong) the Anglo-Persian Oil Company s hospitals keep wards at a temperature of 65 F and low humidity for the treatment of these cases Heat pyrexia patients are placed in the cold storage chamber attached to the local ice plant and are taken to the hospital either in the coolest part of the day or at night

Caffeine and aromatic spirits of ammonia are of great value as stimulants Intravenous injection of normal saline and 5 per cent dextrose solution is also helpful Salt is of the greatest value in cases of heat pyrexia and heat cramps and dextrose is also most helpful

and these must be unbroken if the food is to be regarded as completely safe for consumption Before breaking the skins these outer coverings should be washed with soap and water or else with alcohol or weak lysol to make sure that infection is not accidentally conveyed to the food Lettuce and celery should be dipped in boiling water for at least thirty seconds before being served Native foods should be avoided for they are a serious source of danger especially if they are cold

Extreme care should of course be exercised in the preparation of food for infants and young children Evaporated and dried milk are safer than the local whole milk and should be prepared according to the directions of a competent pediatrician

Comfort and cleanliness are imperative in the tropics because of the ever present dangers to health Flies and mosquitoes should be regarded as mortal enemies as indeed they are when they bear with them such diseases as dysentery and malaria Comfort is essential for changed conditions of life involve nervous strain and good health depends on safeguarding nerves and energies from undue stress

LIVING CONDITIONS IN THE TROPICS

Important factors in adjusting to life in the tropics include housing hours of work clothing food and drink Housing should be designed to protect against the heat of the sun and to provide adequate ventilation Double roofs are of great value whereas corrugated iron roofs increase the heat inside the house Trees and plants around the house reduce the reflected light and promote the evaporation of moisture Working hours should be modified in order to allow for a rest period from noon until three or four o clock in the afternoon Heavy physical exercise should be avoided during that period and even if the individual does not sleep he will save himself much nervous stress and strain by resting Clothing should be light and porous and sun helmets that have detached head bands should be worn Food and drink should be carefully selected starches and sugars should be avoided salt should be taken freely and alcoholic beverages taken in moderation or avoided especially during the heat of the day

CHAPTER LXXI

PERSONAL HYGIENE

Z T BERCOVITZ

PERSONAL ADJUSTMENT TO LIFE IN TROPICAL COUNTRIES involves adapting oneself to conditions that are for the most part radically different from life in milder climates Every individual should undergo a thorough physical examination before going to live in the tropics If chronic disease is present it may be advisable to change one s plans for people suffering from chronic illness are not as a rule able to stand the strain of the new conditions Prophylactic injections are available now for such diseases as small pox yellow fever typhoid paratyphoid diphtheria and scarlet fever typhus cholera and plague These should be taken if indicated to provide as much protection as science is able to afford in the face of these diseases Prophylactic measures can also be taken for malaria The daily routine of life should be altered to meet new conditions In particular energy has to be conserved and this is accomplished by resting from noon until later afternoon and by avoiding late hours and unnecessary physical exertion At least eight hours sleep should be secured each night and bedrooms should have adequate ventilation and protection from mosquitoes and other insects

Clothing should always be light and porous to insure free circulation of the air Materials which hold moisture are to be avoided for reasons of health as well as of comfort Helmets and wide brimmed hats should be worn and particular care should be taken to protect the eyes and the back of the neck

A well balanced diet is important It should have the necessary proteins carbohydrates and fats with adequate vitamins Meats and green leafy vegetables are of great importance in the diet All food should be well cooked and simple and usually adequate supplies of fresh and canned foods are available Especial care must be taken however in the care and preparation of foods owing to the serious risks of contamination from flies or from hands that have been in contact with infected material Water should be boiled and kept in sterilized containers as a precautionary measure and all food should be thoroughly cooked and served on dishes that have been kept scrupulously clean and free from all possible sources of contamination Uncooked foods should be limited strictly to those that have skins or other outer protection

Hala one is a valuable preparation for the purification of water The following directions for its use are given by Strong When travelling it is important always to carry plenty of drinking water in canteens or other containers They can be filled with boiled water or the water in them can be chlorinated by the addition of a substance such as halazone Theoretically one tablet of halazone is sufficient to chlorinate one quart (or about 1000 cc) of water But if the water contains organic matter two tablets or even more may be required After putting in the chlorinating substance the canteen should be shaken to promote solution of the tablet One half hour later the canteen should be shaken again Then if enough of the chlorinating substance has been used the odor of free chlorine can be detected by its smell on removal of the stopper If there is no odor of chlorine more of the chlorinating substance should be put in and the procedure repeated

The Lyster bag which is made of canvas sewn to a galvanized iron ring holds 36 gallons of water and is of the greatest value in the tropics It should be set up and filled to within 4 inches from the top with water One gram of chlorinated lime should be dissolved and poured into the water which should then be well stirred and allowed to stand for from fifteen to thirty minutes One gram of sodium hyposulphite may then be added for each 2 gm of chlorinated lime Again stir water and allow to stand before using The sodium hyposulphite combines with the free chlorine to remove the odor and taste from the water

SEWAGE DISPOSAL

Sewage refers to either liquid or solid excreta that may be mixed with other liquid or solid waste from houses and other buildings The proper disposal of this material is of the greatest importance to the health of the community In tropical villages and other areas where sanitation methods are primitive especial care must be taken in order to safeguard health Whatever method of disposal is used care should be taken to prevent flies from gaining access to the sewage Covers for privies and a supply of lime or dirt should be provided for this purpose Septic tanks are more satisfactory than other and more primitive conveniences

FLIES

Poisons and sticky fly papers are of value in the destruction of flies An effective poison can be made by adding three teaspoonfuls of commercial formalin to a pint of milk or water which should be sweetened with brown sugar Partly fill a drinking glass with this mixture then cut a piece of white blotting paper the size of a dish and place it bottom up on the glass invert the whole quickly and place a small match stick under the edge of the glass

Prevention of fly breeding is important and for this purpose manure piles may be treated with hellebore using a watery extract of 1/ pound to 10 gallons of water which should have been allowed to stand for twenty four hours This is sprinkled over the manure in proportions of 10 gallons to every cubic foot

CHAPTER LXXII

SANITATION

Z T BERCOVITZ

WATER

IN MOST TROPICAL COUNTRIES THE MAIN SOURCES OF water supply are rain water springs shallow and deep wells streams and surface water that has gathered in pools Wherever it gathers the water is subject to pollution from night soil and other excreta that come into direct or indirect contact with it The various types of parasite that are found in polluted water cause infection by ingestion or by penetration of the unbroken skin

Rain water is the purest form of water but if it is to be protected from pollution it should be made to flow into concrete cisterns that should be water tight and covered with an overflow directly to the outside All intake and out flow pipes should be carefully screened for protection against mosquitoes Rain water protected in this manner is safe to drink as it stands

Wells should be so placed that there will be no drainage either from the surface of the ground or from septic tanks and privies to pollute the water Springs are a satisfactory source of water supply but they should be regarded with suspicion and the water should be boiled

The safest method of purification of the water supply is by boiling and when traveling in the tropics people should carry boiled water in sterile containers Sedimentation and filtration are other methods adopted for making water fit for human consumption Numerous chemicals are also used for the same purpose *Potassium permanganate* although seldom used is thought to be of value in the destruction of cholera vibrios *Sodium bisulphate* used in amounts of 15 grains to a pint of water depends on the liberation of free sulphuric acid for its potency *Iodine* may be used in quantities of 1 drop to a liter of water *Chlorine* is a satisfactory chemical for this purpose but too much chlorine gives an unpleasant taste to the water and may cause diarrhea A stock solution for the chlorination of water in the field is prepared by adding one half teaspoon ful of chlorinated lime to a pint of water This solution should be freshly made from a good grade of chlorinated lime that has a strong odor of chlorine Moist caked or lumpy chlorinated lime is generally low in chlorine

soft soap 1 part and water 5 parts The soap is dissolved in the water by heating Then the kerosene is gradually stirred into the hot mixture

LICE

The eradication of lice is of great importance Head lice are treated by cropping the hair close to the head and cleansing it by wiping the nits off with a solution of 1 30 phenol and by rubbing into the back of the head unguentum hydrargyri ammoniati diluted (10 grains to 1 ounce) or any fatty sticky body For the destruction of body lice all body and bed linen and clothes are to be baked or sterilized by boiling unguentum staphisagriae is to be applied to neckbands or vests and shirts in the region of the neck and alkaline baths are to be taken to soothe irritated skin A kerosene emulsion soap to be used in the bath is made by boiling 1 part soap 4 parts water and then adding 2 parts kerosene oil This results in a jelly which when mixed with 4 parts of water makes a useful liquid soap Following the bath the body should be rubbed over carefully with kerosene but this may have to be removed if skin irritation develops Preventive dusting powders may also be used

of manure This mixture will kill from 88 to 99 per cent of the larvae but it may be poisonous to live stock Powdered borax in proportions of 1 pound to 16 cubic feet will kill about 90 per cent of the larvae if the borax is spread evenly over the manure and the water is sprinkled over the borax and manure Garbage and other material also attract flies and should be treated accordingly

Sprays to be used as insecticides may be made from pyrethrum flowers (powdered or coarsely ground) mixed with kerosene or turpentine in quantities of 1 pound of pyrethrum to 1 gallon of oil The mixture is allowed to stand for two or three days and is then percolated once

MOSQUITOES

The problems of antilarval methods and of mosquito destruction are fully discussed in textbooks on sanitation Oiling and spraying of antilarval dusts such as Paris green are most commonly employed

BEDBUGS

Temperatures of 96 F to 100 F accompanied by high humidity will kill newly hatched bedbugs within a few days and a temperature of 113 F will kill them within a few minutes The higher temperature will kill the eggs as well Clothing and bedding should be exposed to fresh air and sunlight daily Steam hot water and blow torch are effective when they can be used The pyrethrum and kerosene mixture is lethal in a few seconds and may be applied with brush or spray Badly infested quarters may require fumigation and for this purpose 1 to 10 ounces of potassium cyanide to 1 000 cubic feet should be used The exposure should last for one hour Unless cautiously used this method is dangerous to human life The fumes of burning sulphur will also destroy the insects in all stages of its life cycle An effective dosage is obtained by burning 4 pounds of sulphur for each 1 000 cubic feet of space for at least six hours

RAT FLEAS

Rat fleas and rats must be destroyed at the same time if there is rat flea infestation The rats may be destroyed by fumigation bait poison trapping and by other means Hydrocyanic acid may be used for fumigation but as this method involves danger to human life as well the Health Department suggests the substitution of cyanogen chloride gas instead For fumigation against rats the Public Health Service uses 4 ounces of sodium cyanide 0 8 to 1 6 ounces of sodium chlorate 17 ounces of commercial hydrochloric acid and 17 ounces of water per 1 000 cubic feet of space The acid and water are mixed in barrels crocks or buckets and the sacks containing the dry chemicals are dropped into the mixture by men wearing anticyanide gas masks Eggs containing a mixture of sodium cyanide and sodium chlorate may be purchased

FLEAS

For the destruction of fleas a mixture should be made of crude petroleum (fuel oil) or an emulsion of kerosene oil in proportions kerosene ° parts

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